Gastrointestinal Pathology III.
Large bowel
Peritoneum

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Semmelweis University
http://semmelweis.hu
2nd Department of Pathology

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

COLON

1. Congenital anomalies
   - Hirschprung disease, anus atresia
2. „Special" pathology of the region
   - diverticulosis, hemorrhoids
3. Inflammatory conditions
4. Polyps and Neoplasms

PERITONEUM

- Inflammatory diseases
- Neoplasms

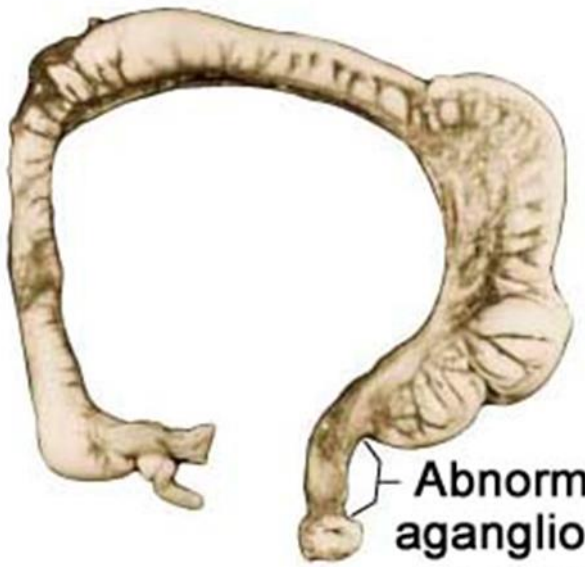
1. Congenital anomalies

Congenital anomalies I.

- Malrotation
  - volvulus in the newborn and ileus (obstruction)
  - Later malabsorption, intermittent obstruction, steatorrhoea
- Stenosis and **atresia**
  - Acquired form occurs more often than the congenital form
    - Cause of stenosis: mucosal diaphragm or stenosed lumen. Possible consequence: intussusception.
    - Atresia: often duodenum or **anus**
- Duplication cysts

Congenital aganglionic megacolon– HIRSCHPRUNG DISEASE (M:F=4:1)

- 1 of 5000 live births
- Lack of parasympathetic ganglia (within both Meissner and Auerbach plexus- no ganglion cells)
- Sporadic or familiar
- Rectum always affected
- Long-segment or Short-segment
- No peristalsis
- Dilation of the bowel proximal to the affected segment-with time megacolon develops

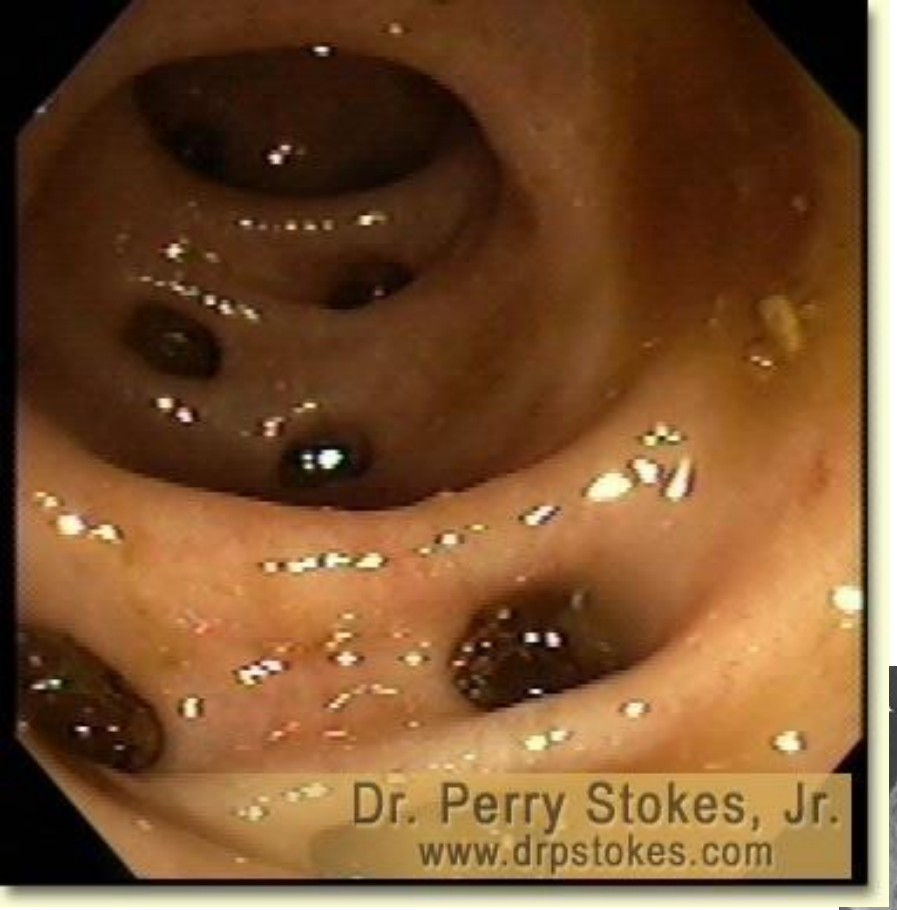


www.yalepath.org/DEPT/ diagunits/pedi_largeint.jpg

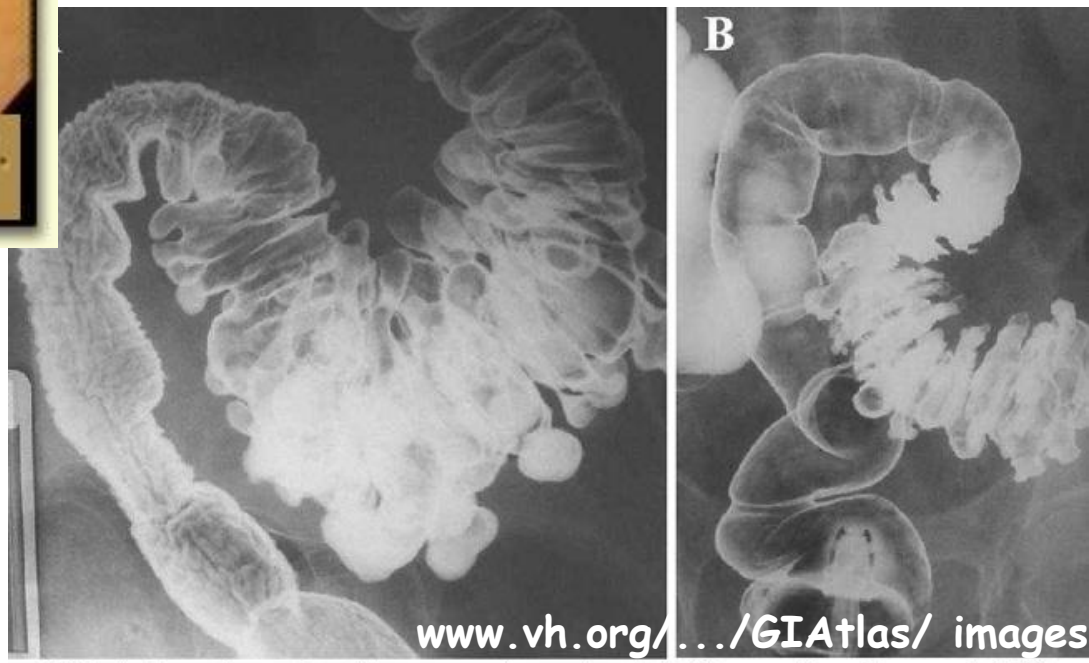
2. „Special" pathology of the region

Acquired diverticulosis

- >60 y
- Disease of developed/industrialised countries
- Cause:
  - low fiber containing diet
- Mucosa outpouching toward the bowel wall, often multiple
- Most common in sigmoid colon
- Complication:
  - diverticulitis, fistula formation, perforation, abscess, hemorrhage



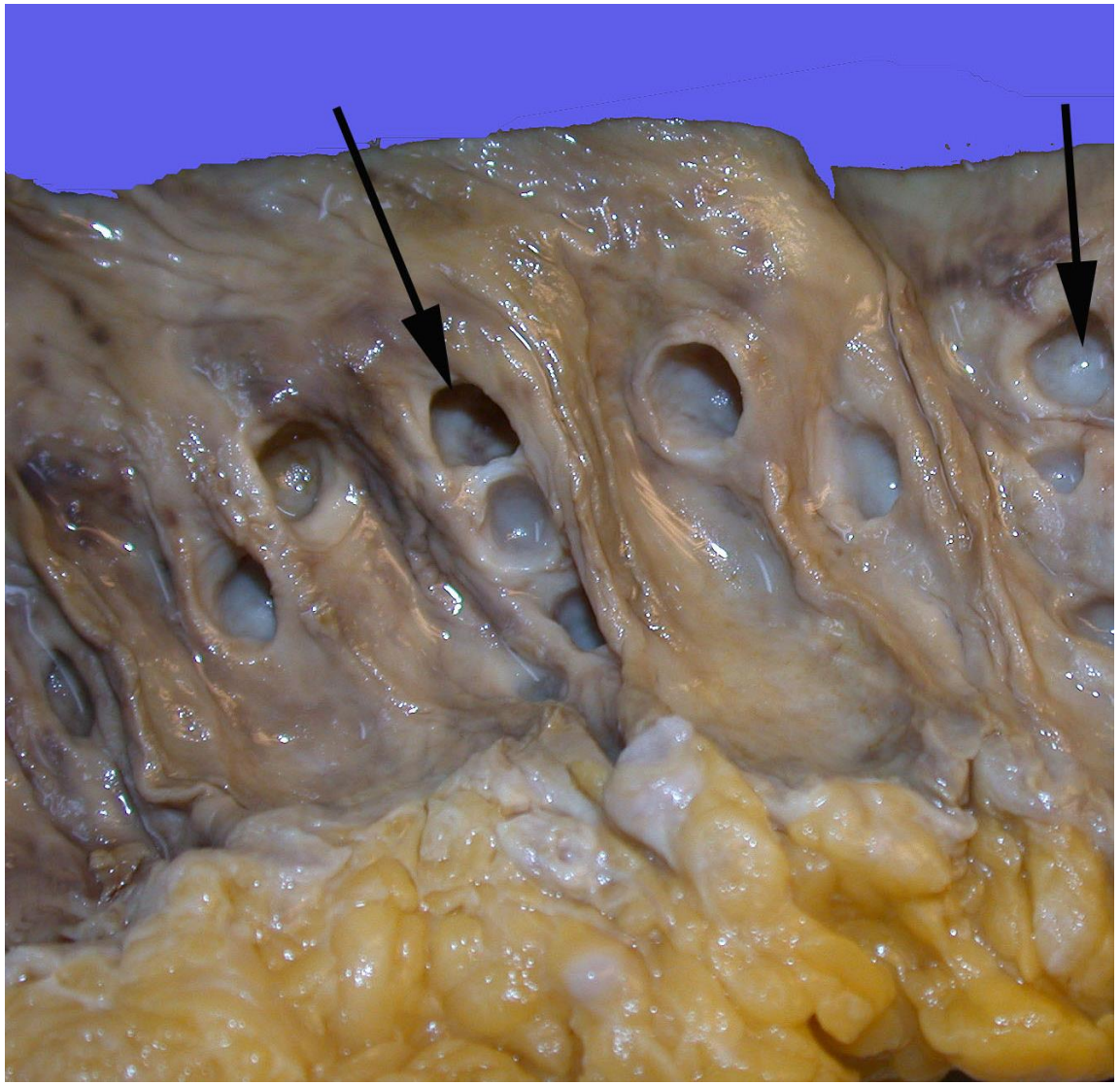
www.fujita-hu.ac.jp/

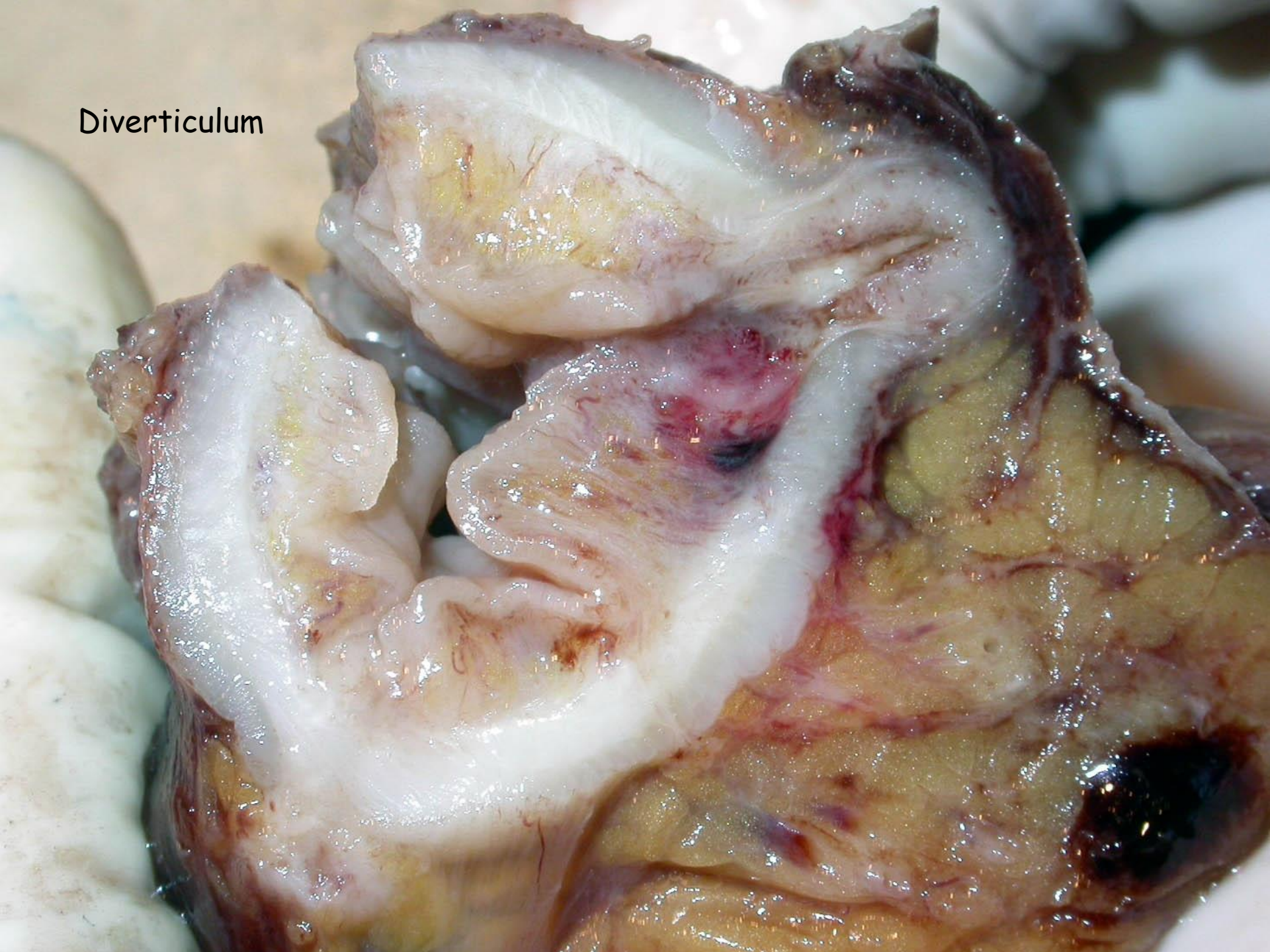


www.vh.org/.../GIAtlas/ images

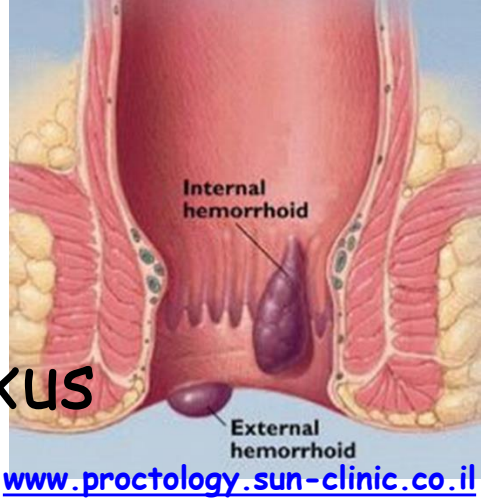
Distal colon in the contracted (A) and relaxed (B) state in a patient with diverticulosis.

Diverticulosis coli




Diverticulum

Hemorrhoids



- Ectatic anal and perianal venous plexus
- Common
- Predisposing factors:
  - sedantery life/profession, overweight, constipation, pregnancy and labour
- In case of hematochesia, even in the presence of visible, hemorrhagic hemorrhoids, examination of the upper colon segments is compulsory!!

Irritable bowel syndrome

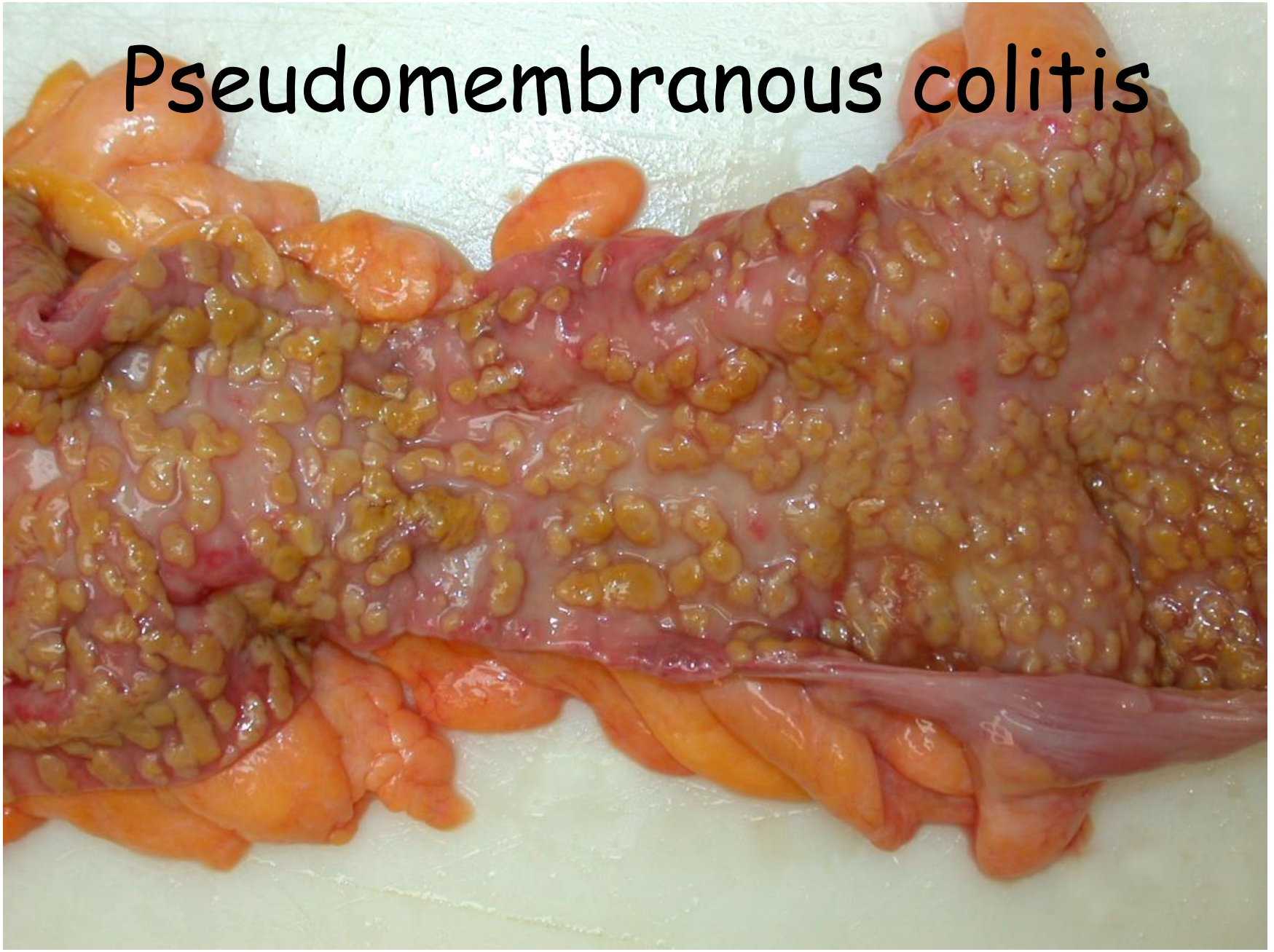
- Chronic abdominal pain, bloating, changes in bowel habit
- MA and MI normal
- 20-40 y women
- Fibromyalgia or other chronic pain disorders, backache, headache,depression, lethargy etc. are commonly associated

3. Inflammatory conditions

Infectious enterocolitis

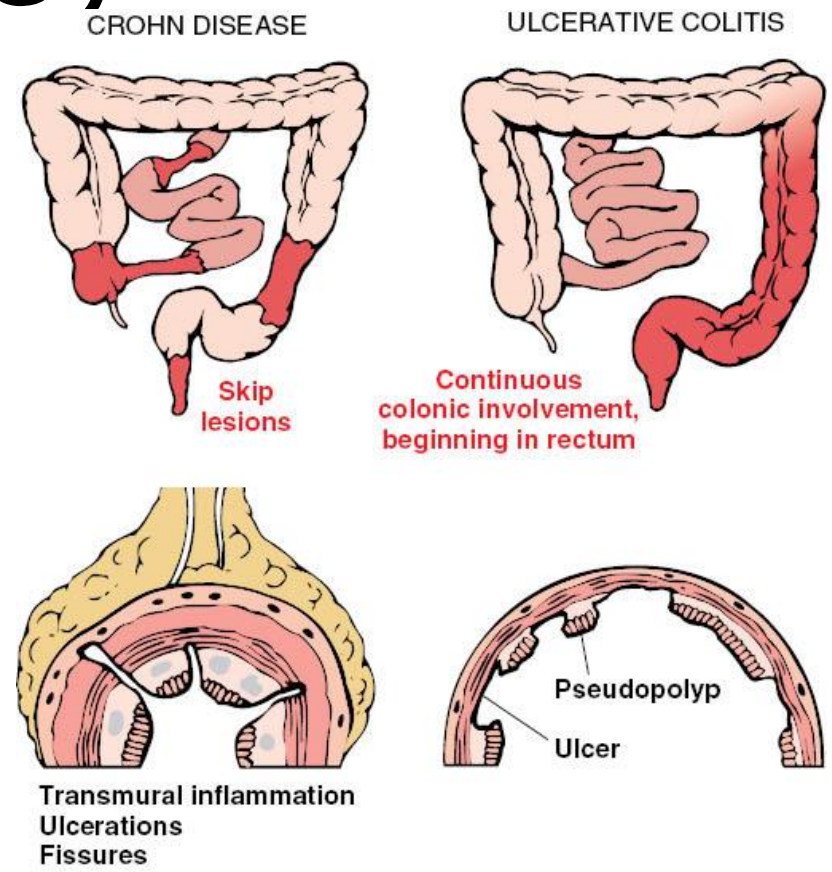
- Viral, bacterial, parasitic – In detail with small bowel
- **Pseudomembranous colitis**
  - Clostridium difficile (in hospitals)
  - Antibiotic-associated (mainly 3rd generation cephalosporins)
  - MA: Pseudomembrane formation
  - MI: Volcano-like eruption of a mucopurulent exudate from damaged crypts, denuded surface epithelium, neutrophils within lamina propria
  - SY: fever, cramps, watery diarrhea, occult blood

Pseudomembranous colitis



Inflammatory Bowel Disease (IBD)

- Crohn disease (CD), Ulcerative colitis (UC)
- Distinction is based on affected **sites/ disease distribution** and **depth** of involvement
- UC-rectum and colon , mucosa and submucosa
- CD- any area of GI (ileal involvement frequent), transmural



IBD- Etiology

- Females
- Teens, early 20s
- Caucasians, Ashkenazi Jews- 3-5x
- Incidence on the rise worldwide
- Hygiene hypothesis: pathogens (that should lead to self-limited disease) trigger immune responses and chronic disease in susceptible host

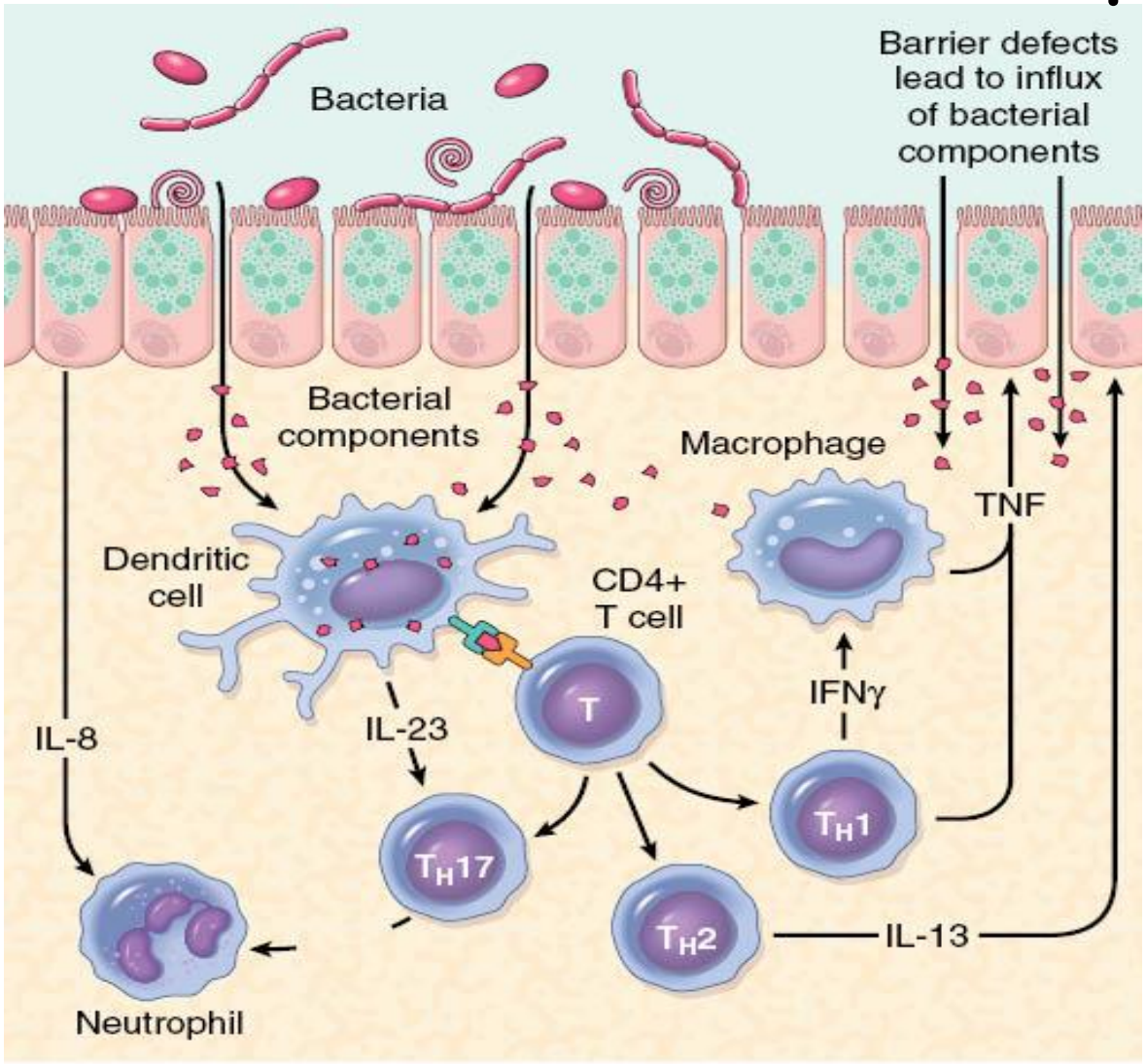
IBD-Pathogenesis

- Idiopathic
- Not autoimmun
- Combination of
  - defects in host-microbe interaction
  - intestinal epithelial dysfunction
  - aberrant mucosal immune response

IBD- Genetics

- Concordance in monozygotic twins: CD - 50%, UC-16%
- Susceptibility gene in CD: **NOD2** (nucleotide oligomerization binding domain 2)
- Polymorphism of NOD2 → 4X inceased risk of CD
- Other genes in CD: **ATG16L1** (Autophagy related 16-like) **IRGM** (Immunity related GTPase M)
- These genes play a role in **recognition** and **reaction** to intracellular pathogens

IBD- Microbiota and Mucosal immune responses



Crohn disease

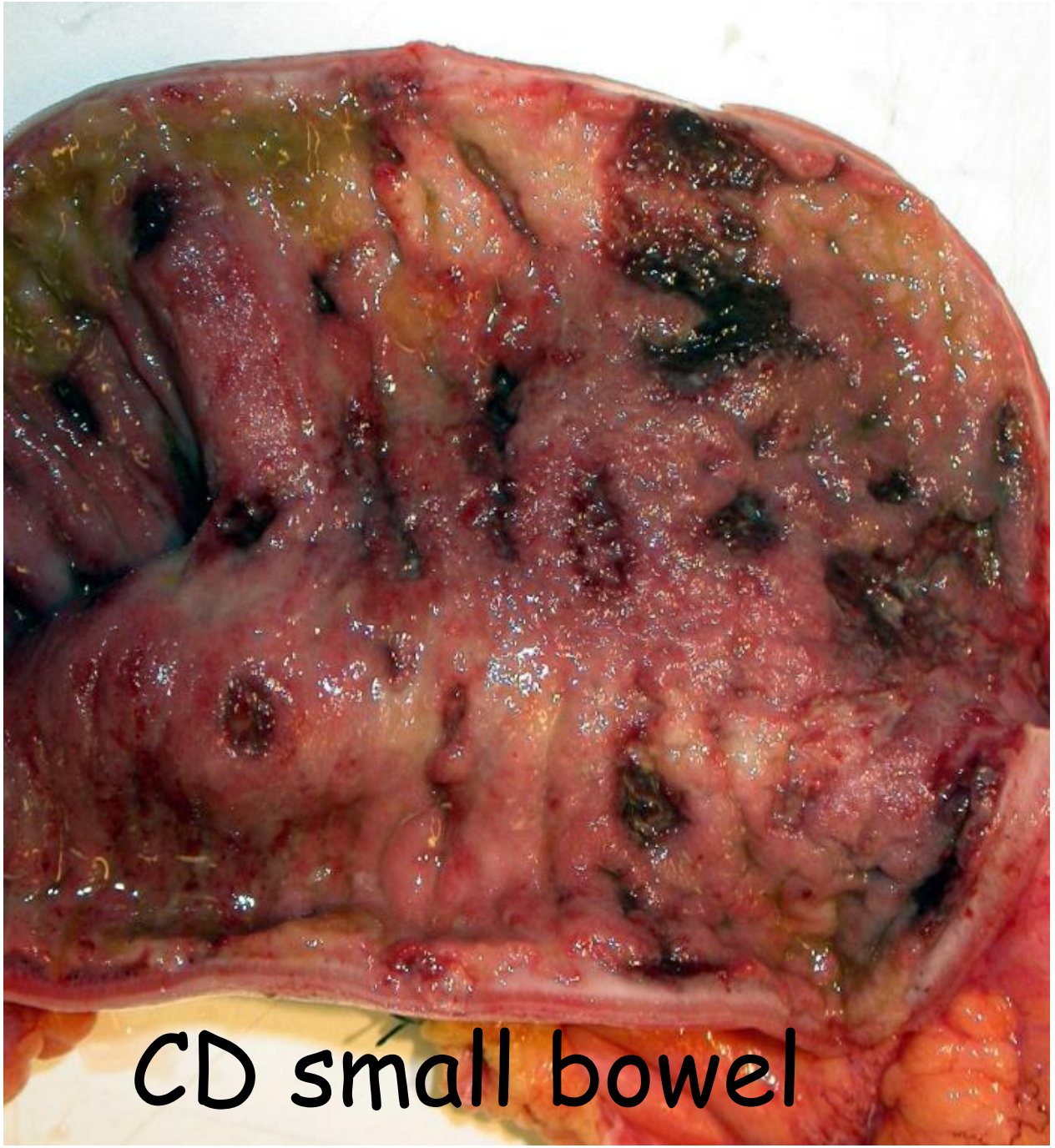
- 1932 by Crohn, Ginzburg and Oppenheimer
- Louis XIII of France (1601-1643)- bloody diarrhea, small intestinal and colonic ulcers, rectal abscesses, fistulae from age 20y
- Any area of GI
- Most commonly involved at disease presentation : terminal ileum, ileocecal valve and cecum
- Small bowel only - 40%
- Small and Large bowel - 30%
- Skip lesions

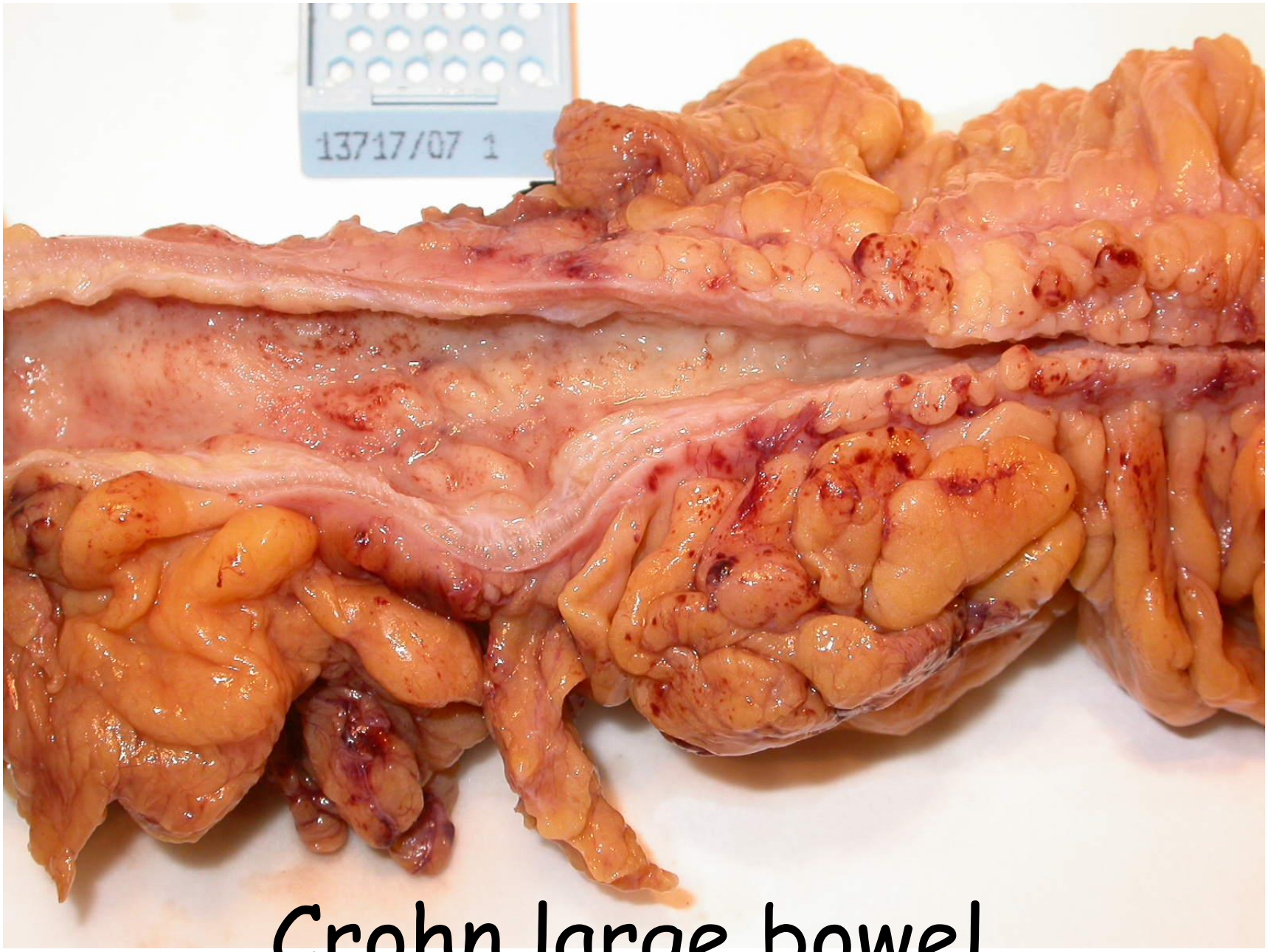
IBD - Epidemiology

- **Crohn disease**
  - Worldwide, common in developed countries
  - The most common in 2nd 3rd and 6th 7th decades, but may occur at any age
- **Ulcerative colitis**
  - In developed countries more common than CD
  - The most common at the age of 20-25 y, but may occur at any age

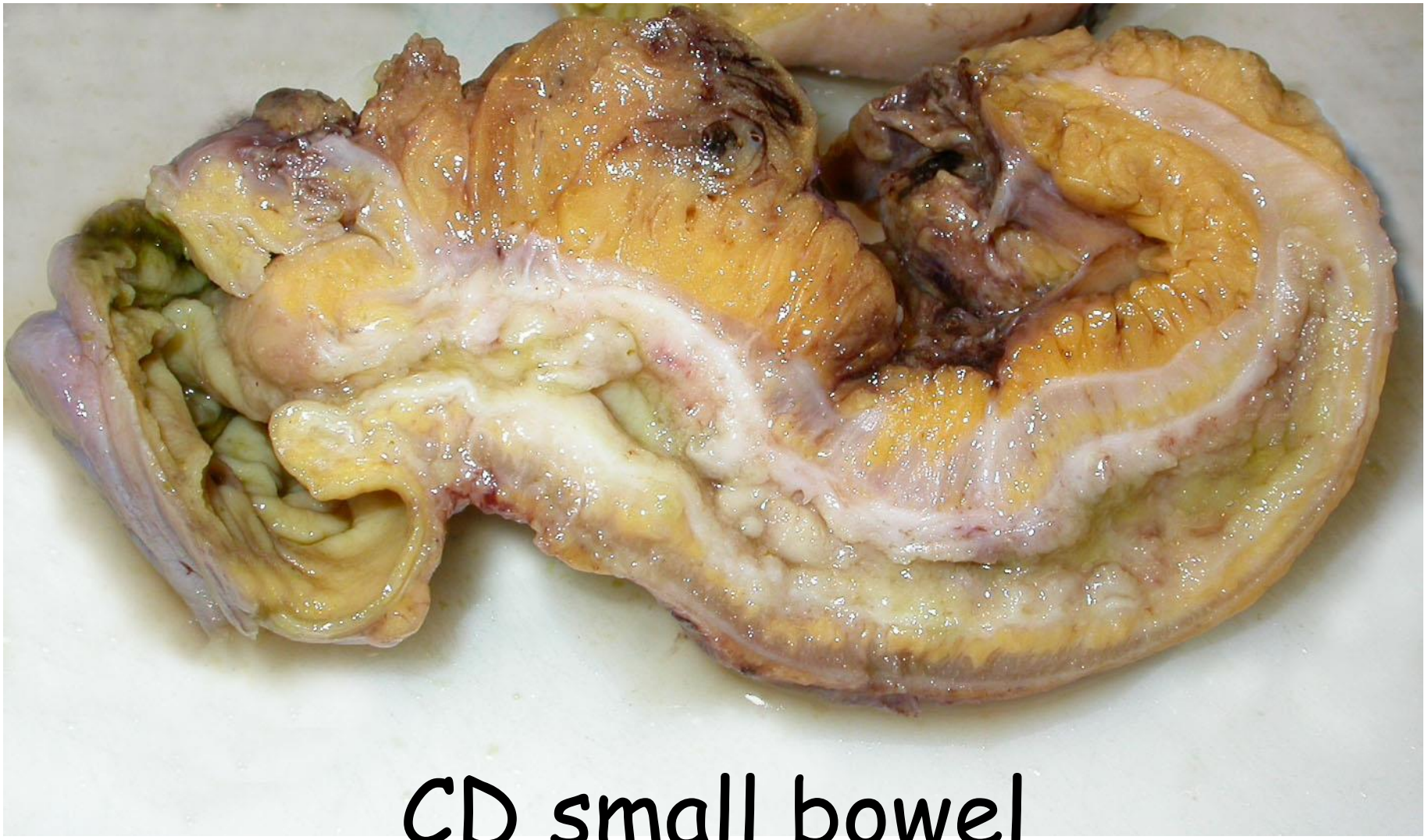
CD- Macroscopy

- **Aphtous ulcers** may coalesce into serpentine ulcers along the axis of the bowel
- **Cobblestone** appearence of mucosa- due to patchy distribution of the inflammation (diseased areas are depressed)
- Fissures, fistulae between loops, toward skin, vagina, urinary bladder etc.
- Intestinal wall thickened (inflammation, fibrosis)
- Strictures, stenoses
- Creeping fat (mesenteric fat extends around serosa)


CD small bowel

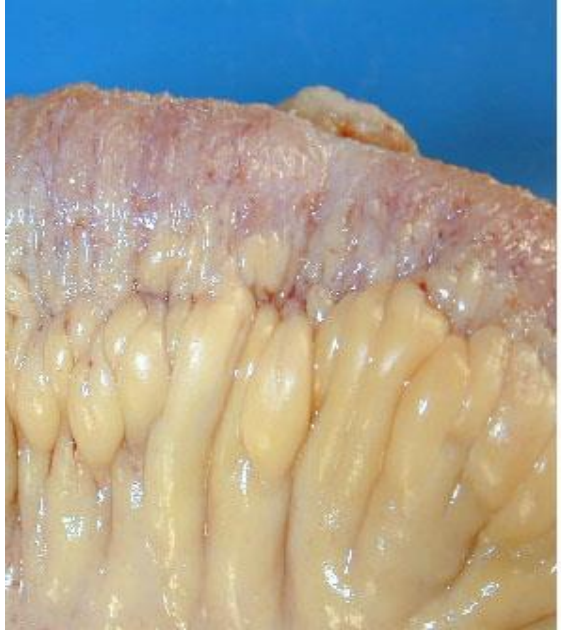


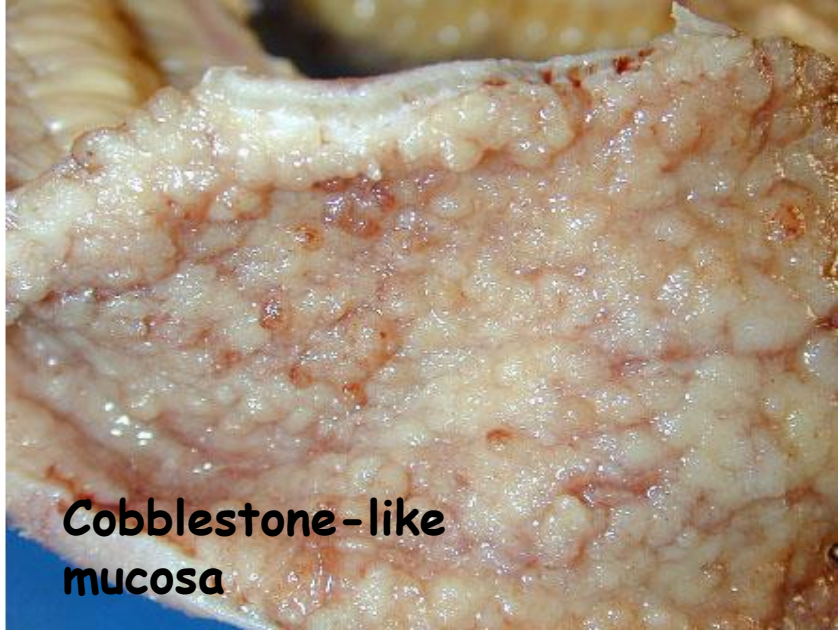
Crohn large bowel

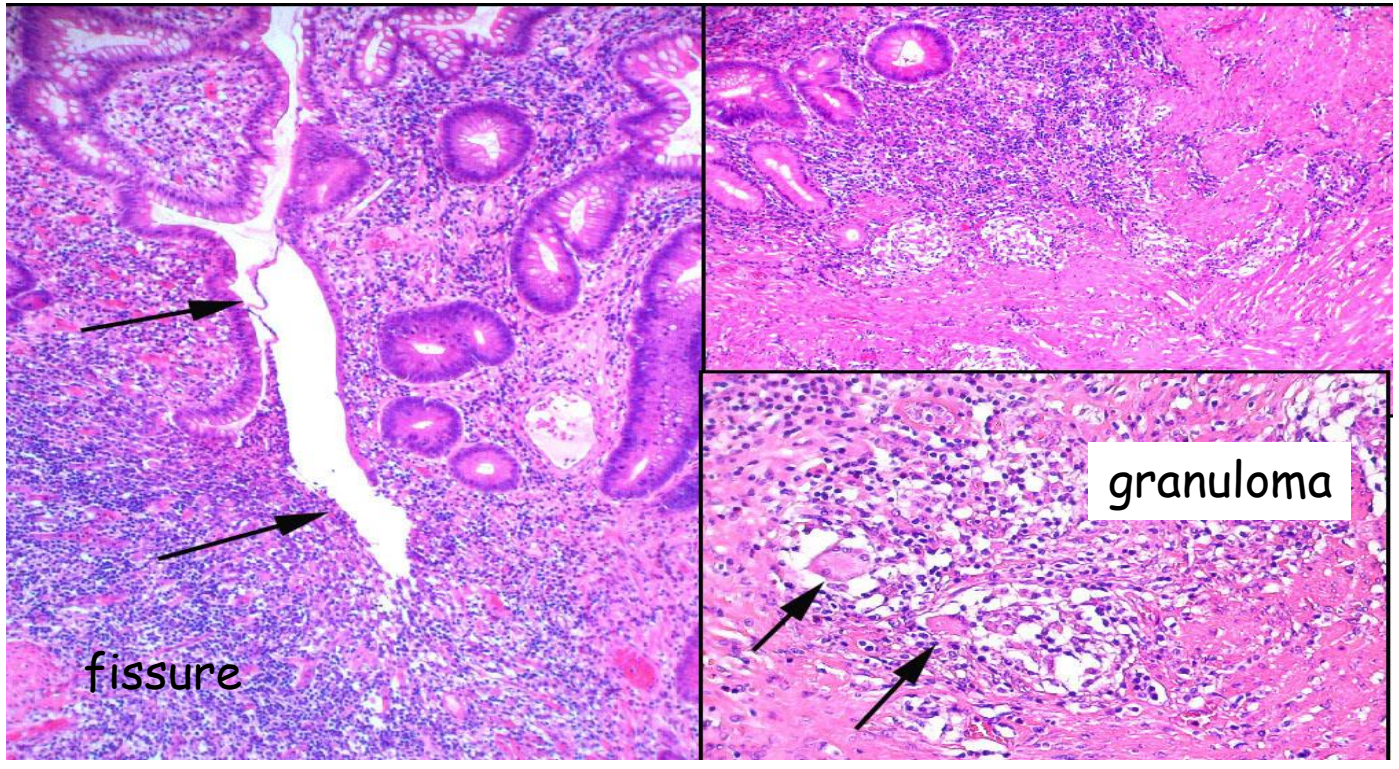


CD small bowel

Crohn disease







CD Microscopy

- **Transmural** inflammation
- Noncaseating **granulomas**: 35% of cases
- Neutrophils damage crypt epithelium- **crypt abscesses**
- Deep, knife-like **ulceration**
- Destruction and regeneration cycles result in **distorted** crypt architecture
- Paneth cell **metaplasia** in left colon
- Mucosal **atrophy** with time

CD Symptoms

- Diarrhea, fever, pain
- Periods of active disease
- Stress-induced reactivation
- Diet, smoking may trigger (first symptoms after initiating use of cigarettes)
- Iron-deficiency anemia, hypoalbuminaemia,malabsorption
- Cheilitis granulomatosa
- Merkelson-Rosenthal syndrome

CD Extra-intestinal manifestation

- Uveitis
- Migratory polyarthritis
- Sacroileitis
- Ankylosing spondylitis
- Erythema nodosum

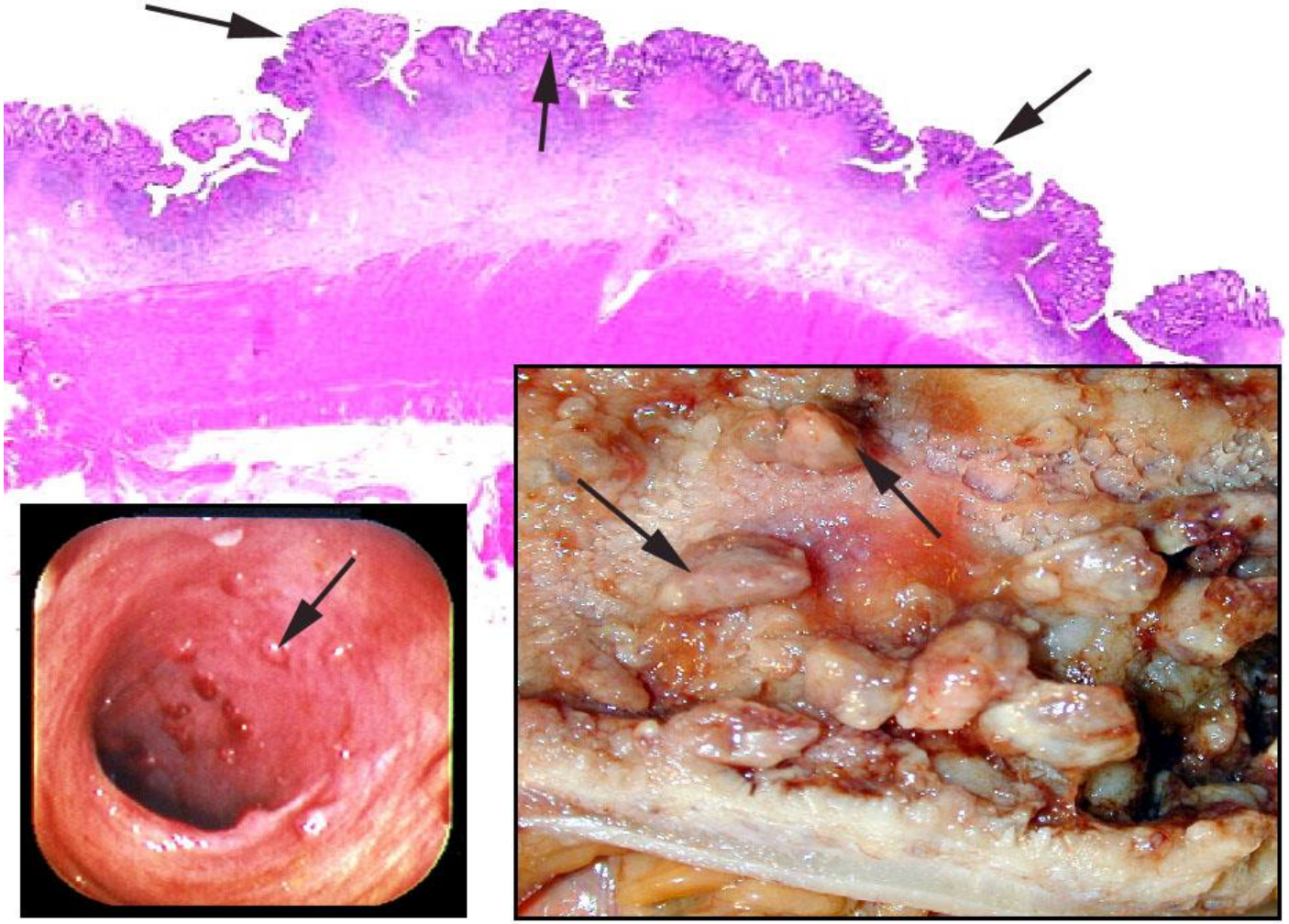
Ulcerative colitis- Macroscopy

- Rectum and colon
- Pancolitis-when the entire colon is affected
- Backwash ileitis in pancolitis-otherwise the small bowel is spared
- Broad-based ulcers
- Isolated islands of regenerating mucosa-pseudopolyps
- Since the disease is not transmural-no thickening of the wall, no strictures
- Toxic megacolon-perforation

UC- Microscopy

- Architectural distortion
- Mucosa, submucosa superficially inflamed
- Neutrophils, crypt abscesses
- Ulcers
- Mucosal atrophy with time
- No granulomas

Ulcerative colitis (pseudopolyps)



UC-Symptoms

- Bloody diarrhea with mucus
- Lower abdominal pain, cramps
- Even the first presentation can be so severe as to present as a medical emergency
- Relapses
- First symptoms may appear after cessation of smoking

UC Extra-intestinal manifestation

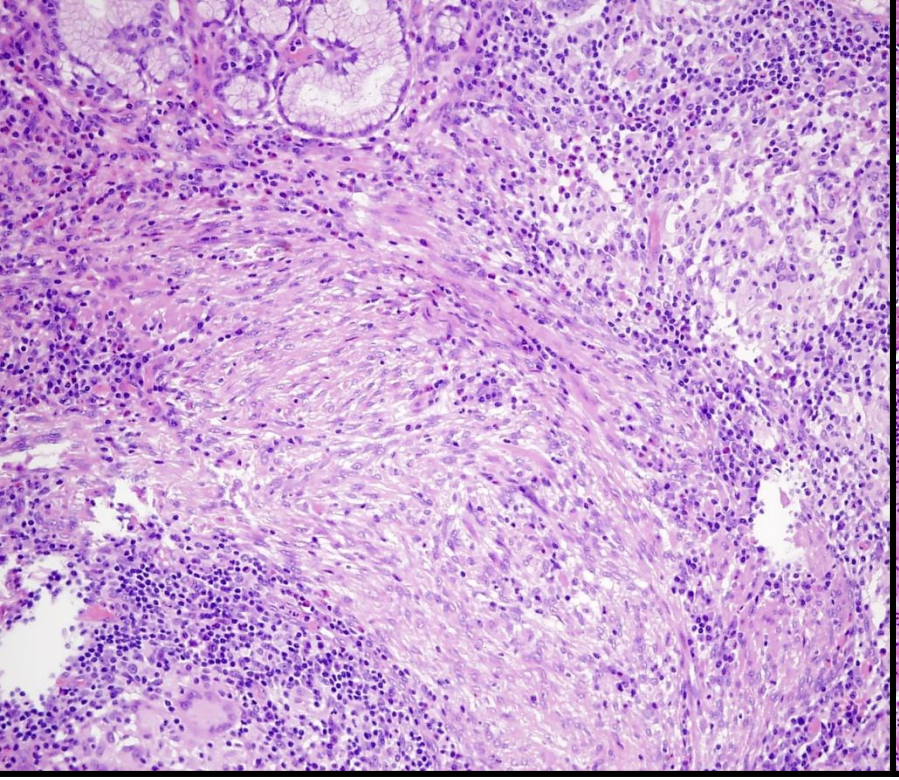
- Uveitis
- Migratory polyarthritis
- Sacroileitis
- Ankylosing spondylitis
- Erythema nodosum

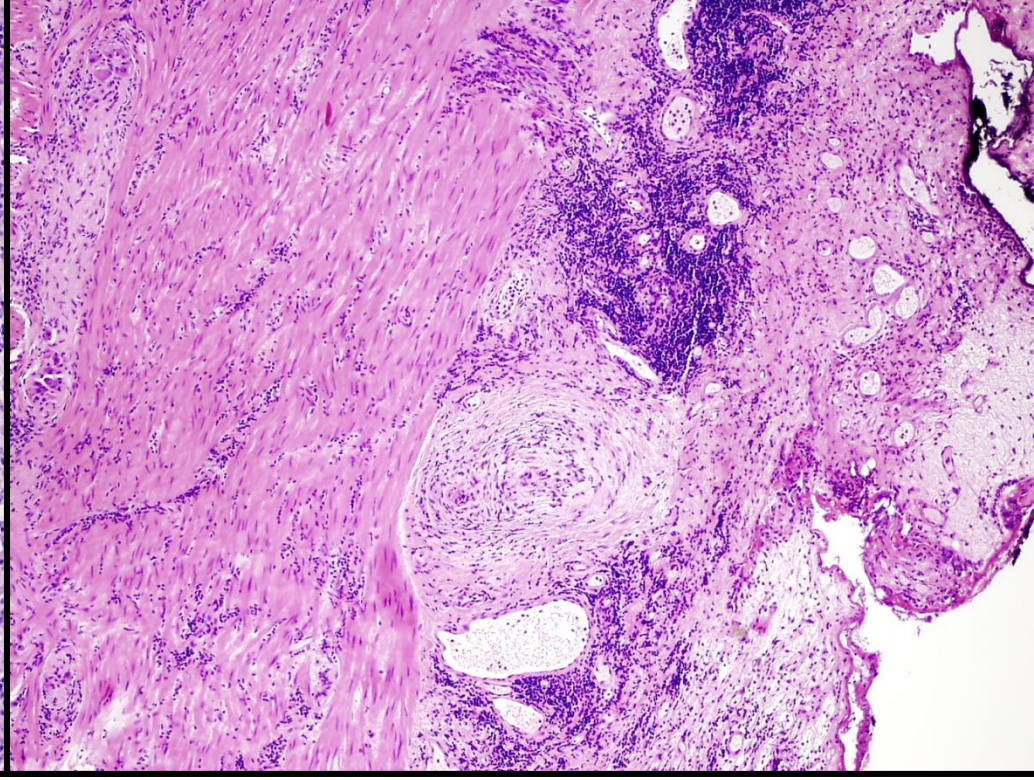
like in CD

- 2,5-7,5% of patients with UC also have **Primary Sclerosing Cholangitis**

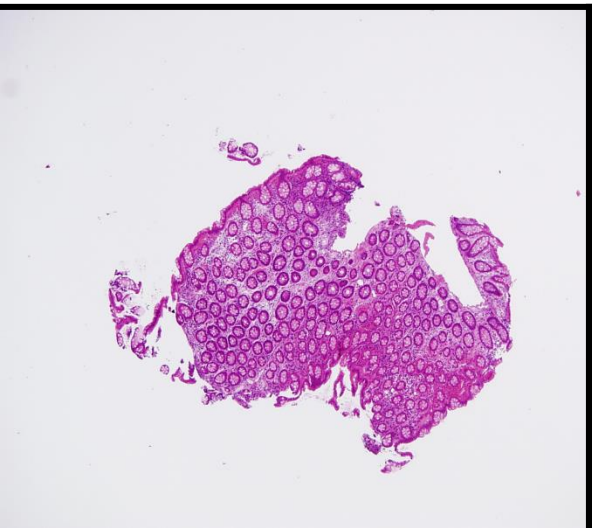
Differences between CD and UC

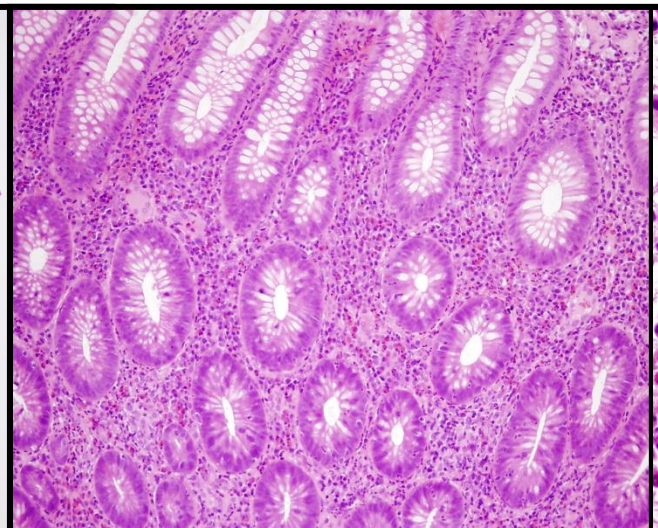
Feature	Crohn Disease	Ulcerative Colitis
Bowel region	Ileum ± colon	Colon mainly
Distribution	Skip lesions	Diffuse
Stricture	Yes	Rare
Wall appearance	Thick	Thin
Inflammation	Transmural	Limited to mucosa
Pseudopolyps	Moderate	Marked
Ulcers	Deep, knife-like	Superficial, broad-based
Lymphoid reaction	Marked	Moderate
Fibrosis	Marked	Mild to none
Granulomas	Yes (~35%)	No
Fistulae/sinuses	Yes	No
Malignant potential	With colonic involvement	Yes
Toxic megacolon	No	Yes
Fat/vitamin malabsorption	Yes	No

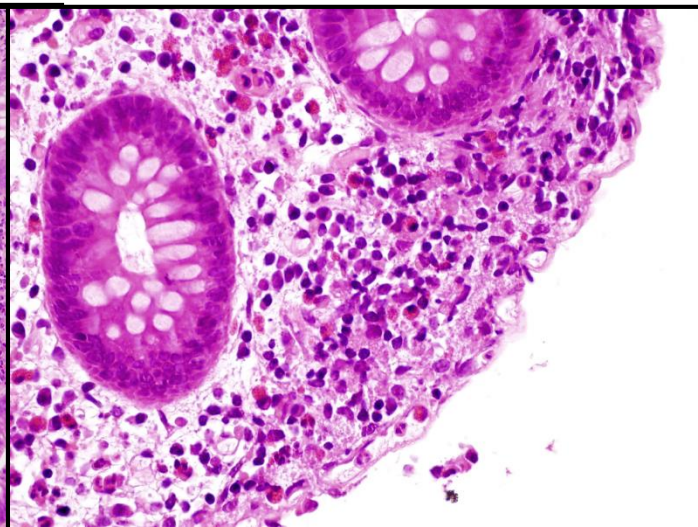


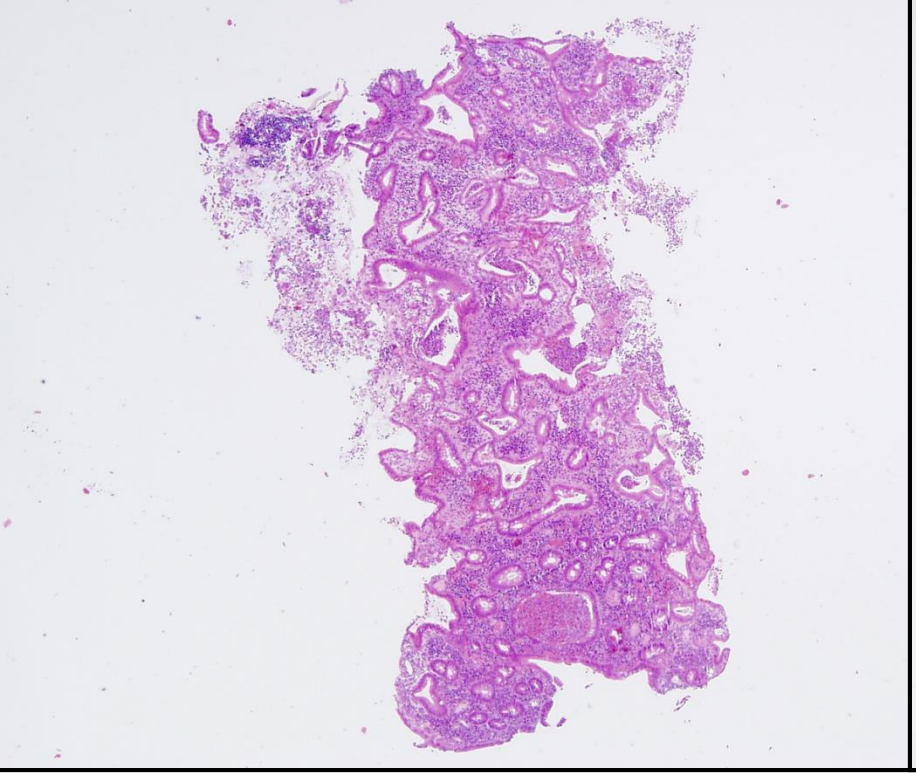


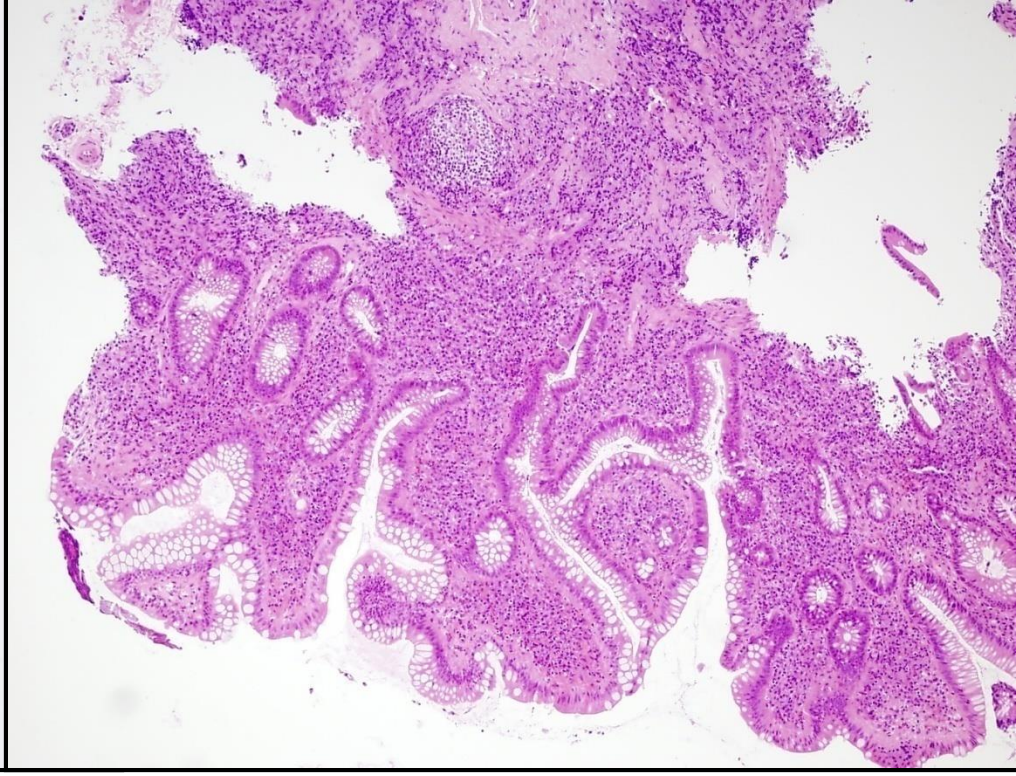
Crohn - disease



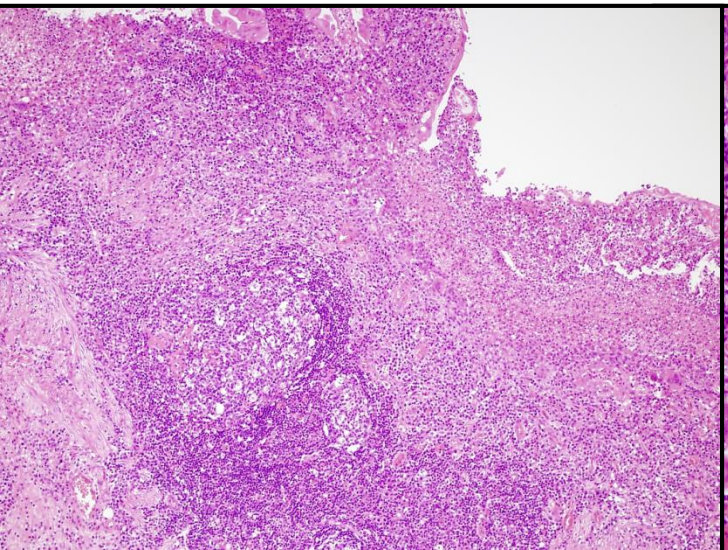


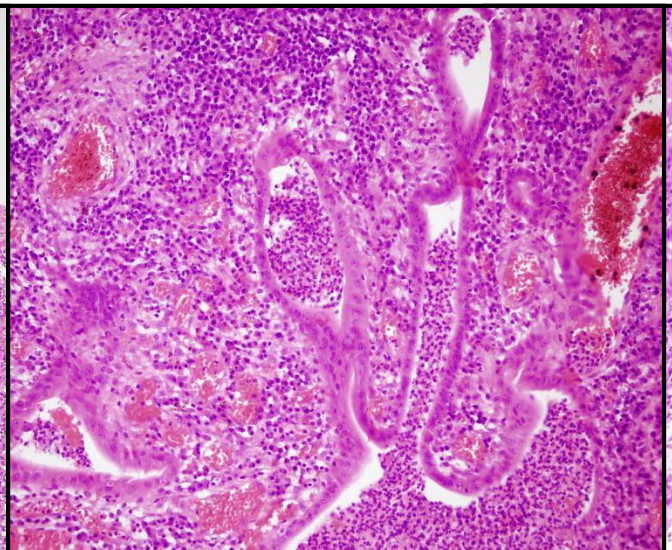


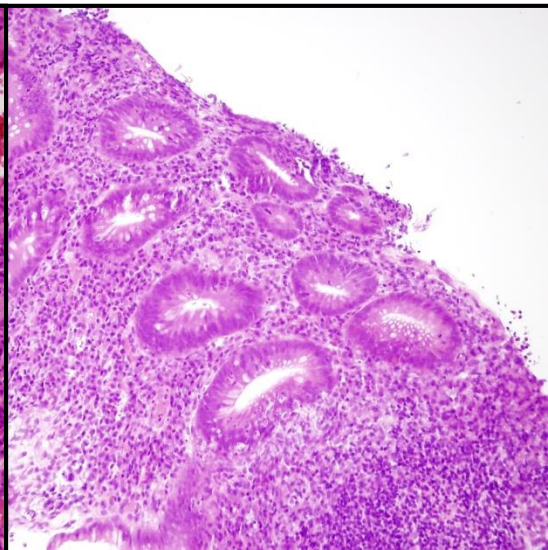




Ulcerative colitis







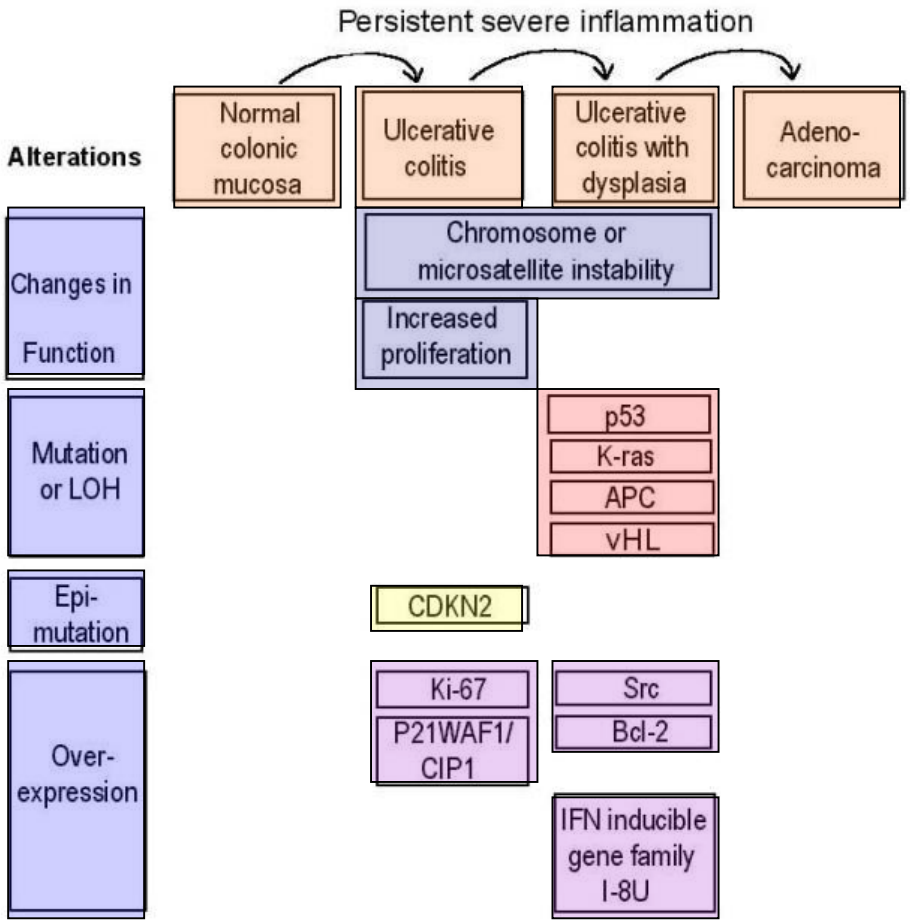
Indeterminate colitis

- 10% of IBD
- Overlaping symptoms and morphology

Colitis-associated neoplasia

- Risk of dyspalsia-neoplasia increases
  - 8-10 years after disease initiation
  - In pancolitis
  - With frequency and severity of active episodes
- Surveillance programs

Carcinoma risk is elevated in ulcerative colitis



1% of colon cancers develops on the ground of ulcerative colitis.

Colon cancer develops in 5% of ulcerative colitis patients.

Other causes of Chronic colitis

- **Diversion colitis-** lymphoid follicles in diverted pouch, sometimes mimics IBD
- **Microscopic colitis**
  - Collagen colitis
  - Lymphocytic colitis
- **GVHD**
  - Small bowel and colon involvement after allogeneic bone marrow transplant presenting as watery diarrhea

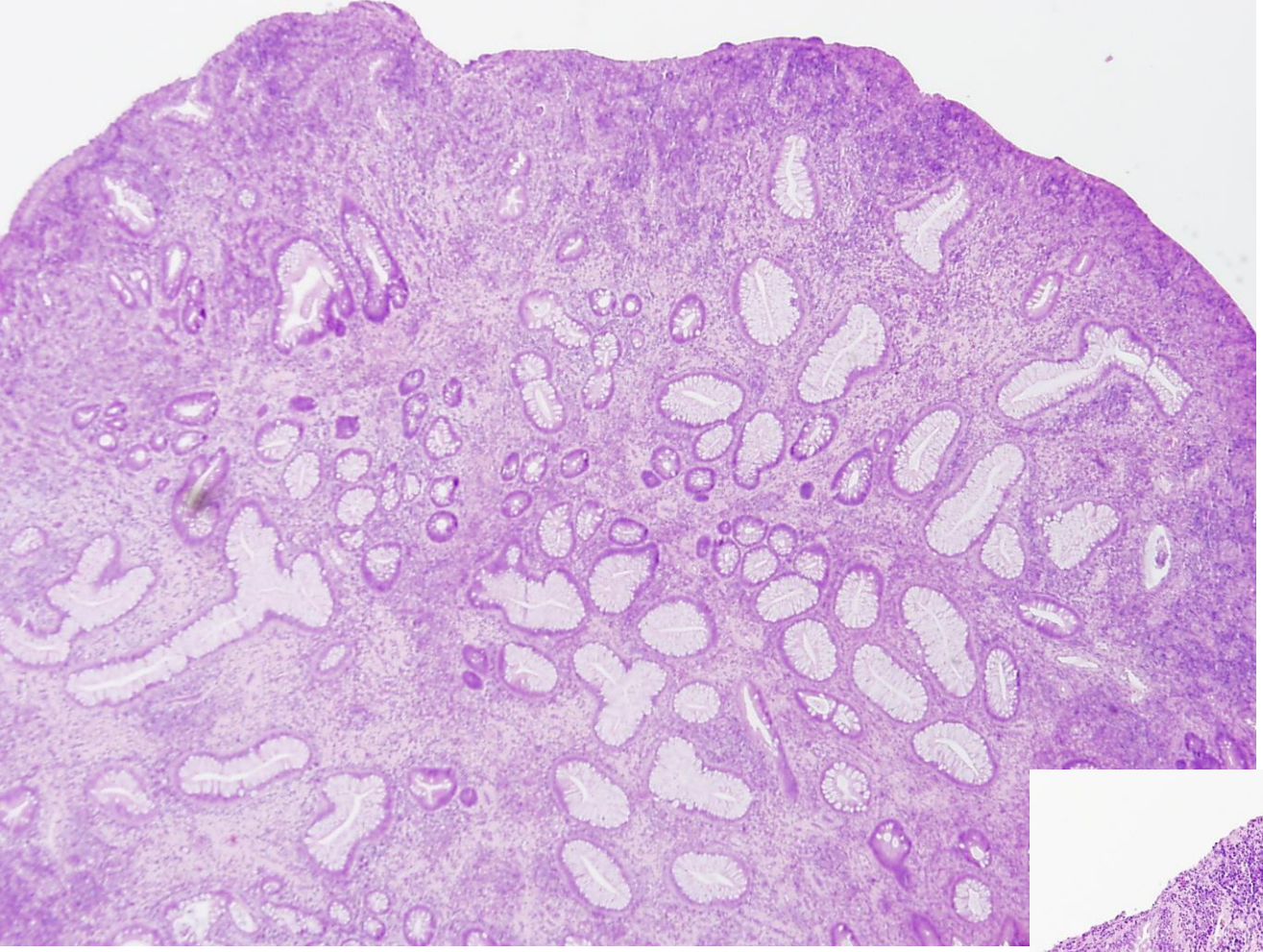
4. Polyps and Neoplasms

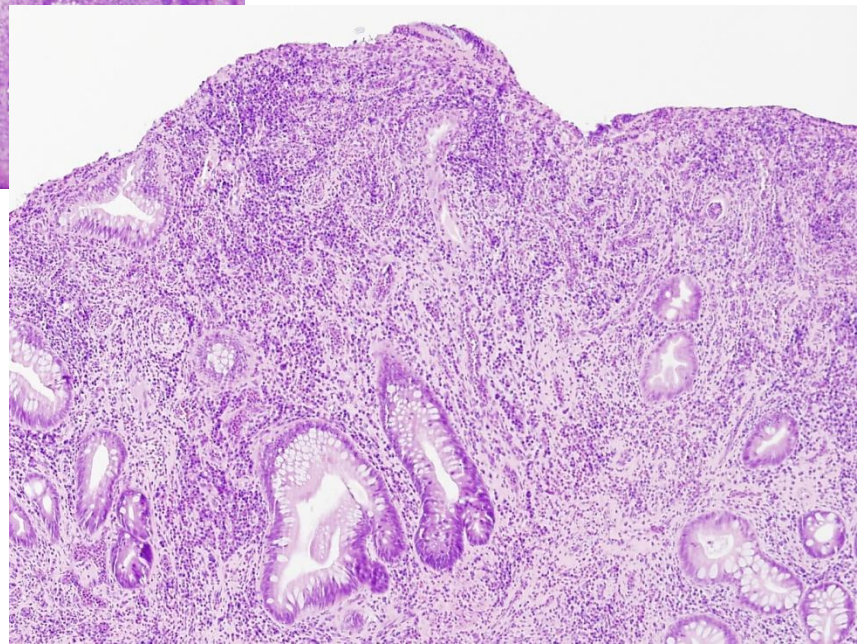
POLYPS

- Polyp is a mass protruding into the lumen of the bowel
- MA: sessile or pedunculated
- Epithelial polyps or polypoid lesions caused by submucosal or mural tumors
- Epithelial polyps : non-neoplastic or neoplastic

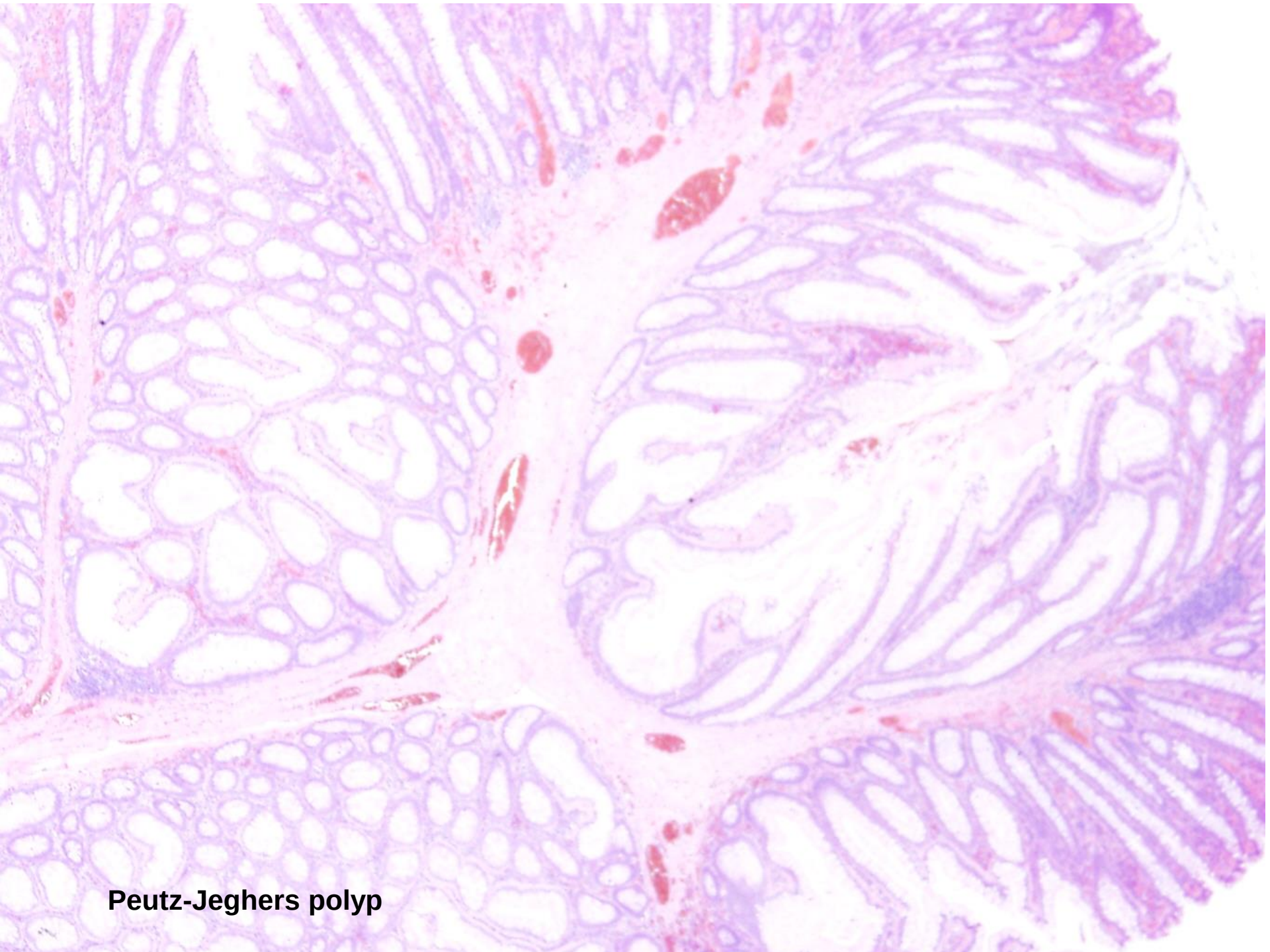
NON-NEOPLASTIC POLYPS I.

- ***Hamartomatous polyps***: malformations of the glands and stroma
  - ***Juvenile polyps:***
    - Children (may occur in adults)
    - Rectum
    - Juvenile Polyposis Syndrome or sporadic polyps
    - cystically dilated glands, inflammation, surface ulceration
  - ***Peutz-Jeghers polyps:***
    - Small bowel, stomach, colon
    - Large polyps
    - normal epithelium, arborizing connective tissue and smooth muscle
    - Sporadic or Peutz-Jeghers sy





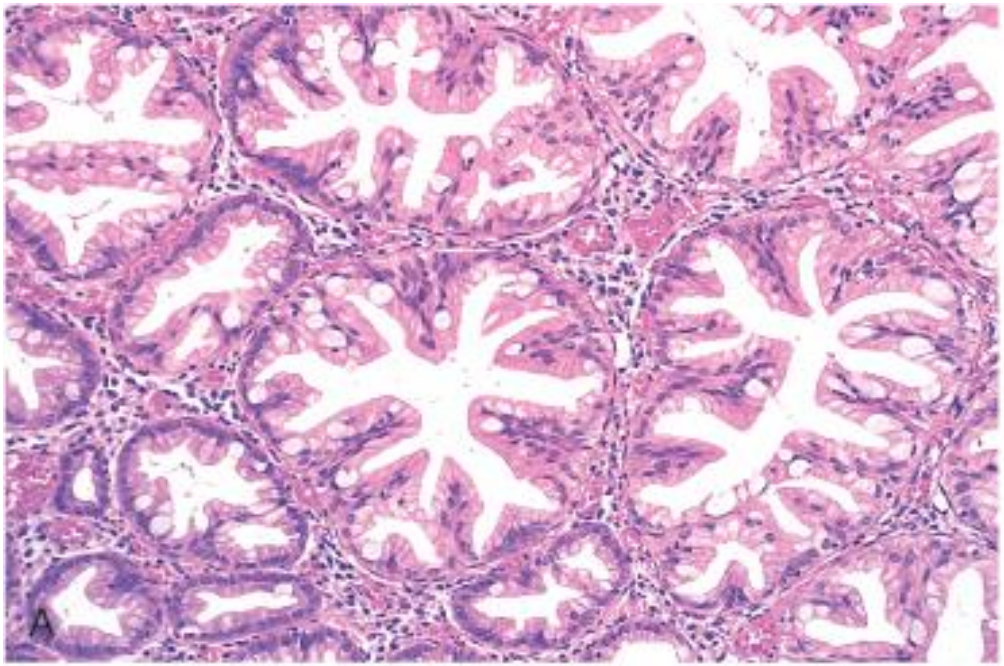
Juvenile polyp



Peutz-Jeghers polyp

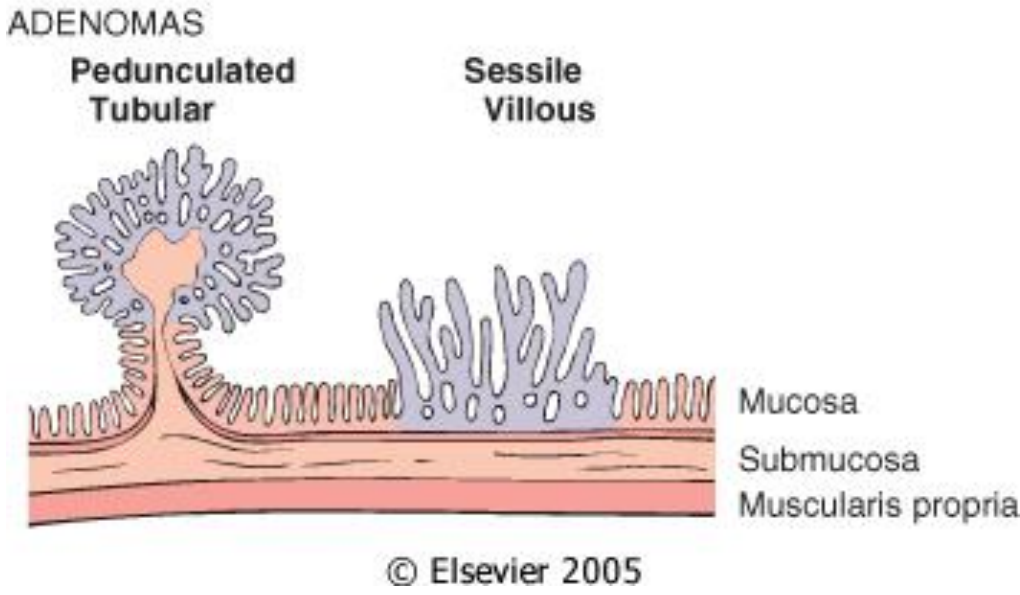
NON-NEOPLASTIC POLYPS II.

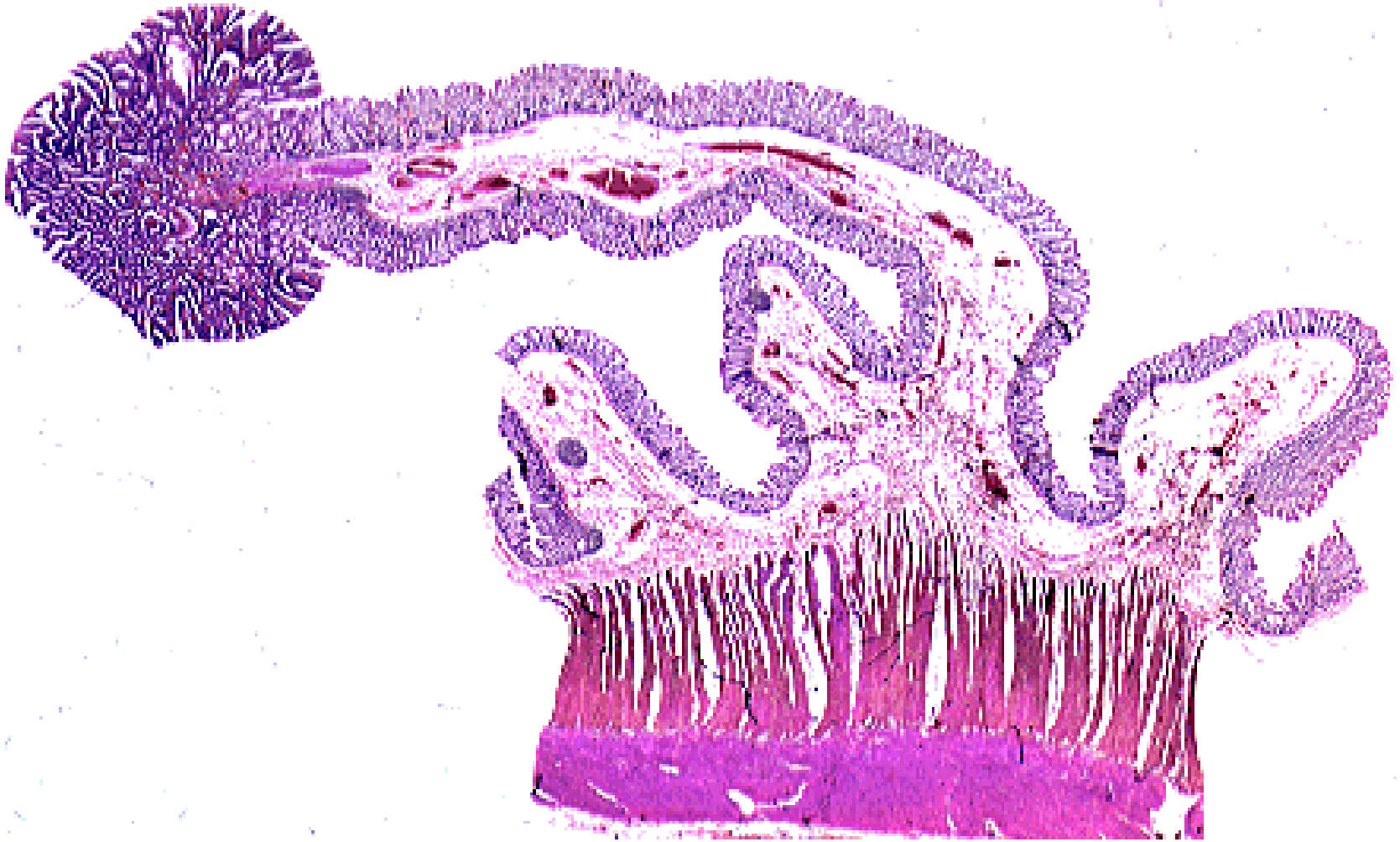
- ***Hyperplastic polyps***
- Left colon
- Frequently multiple
- serrated epithelial structure due to delayed shedding of surface epithelial cells
- malignant potential?
- To distinguish from SESSILE SERRATED ADENOMAS!!!!



NEOPLASTIC POLYPS- Mucosal low- or high grade neoplasia (adenomas) I.

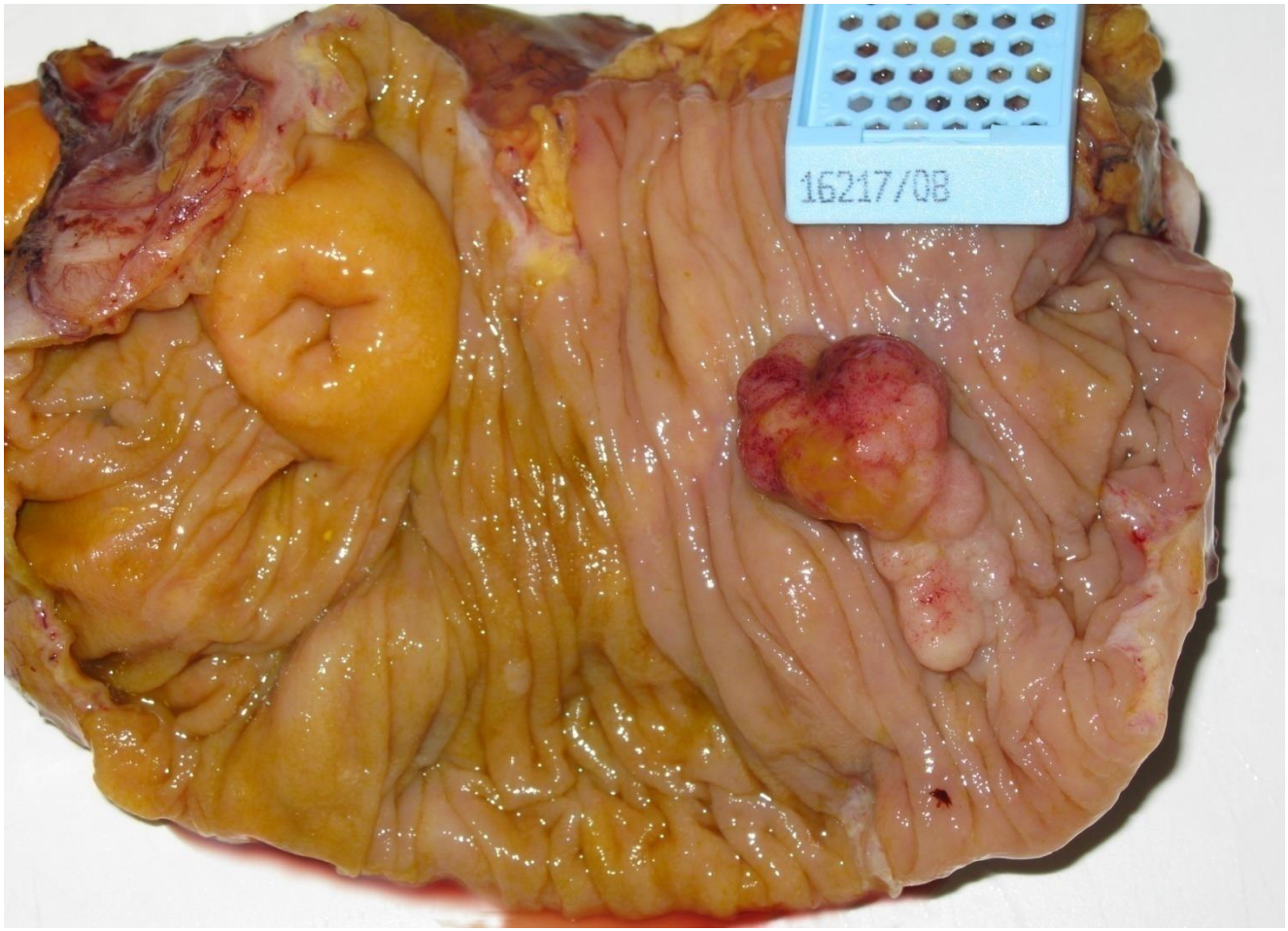
- Precursor lesions of Colorectal Cancer (CRC)
- Surveillance colonoscopy by age 50
- Pedunculated or sessile
- Low grade or high grade dysplasia
- (TUBULAR ADENOMA): 75% tubular structures
- (VILLOUS ADENOMA): at least 50% villous
- (TUBULOVILLOUS): 25-50% villous structures



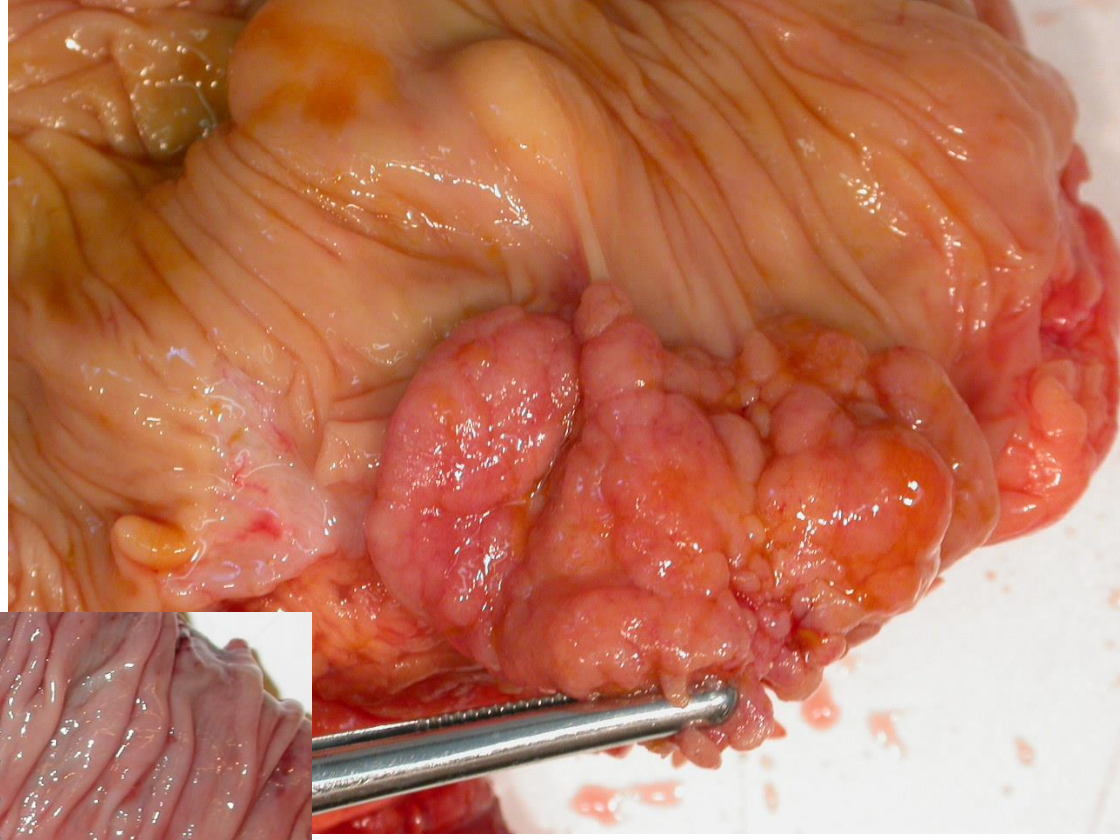


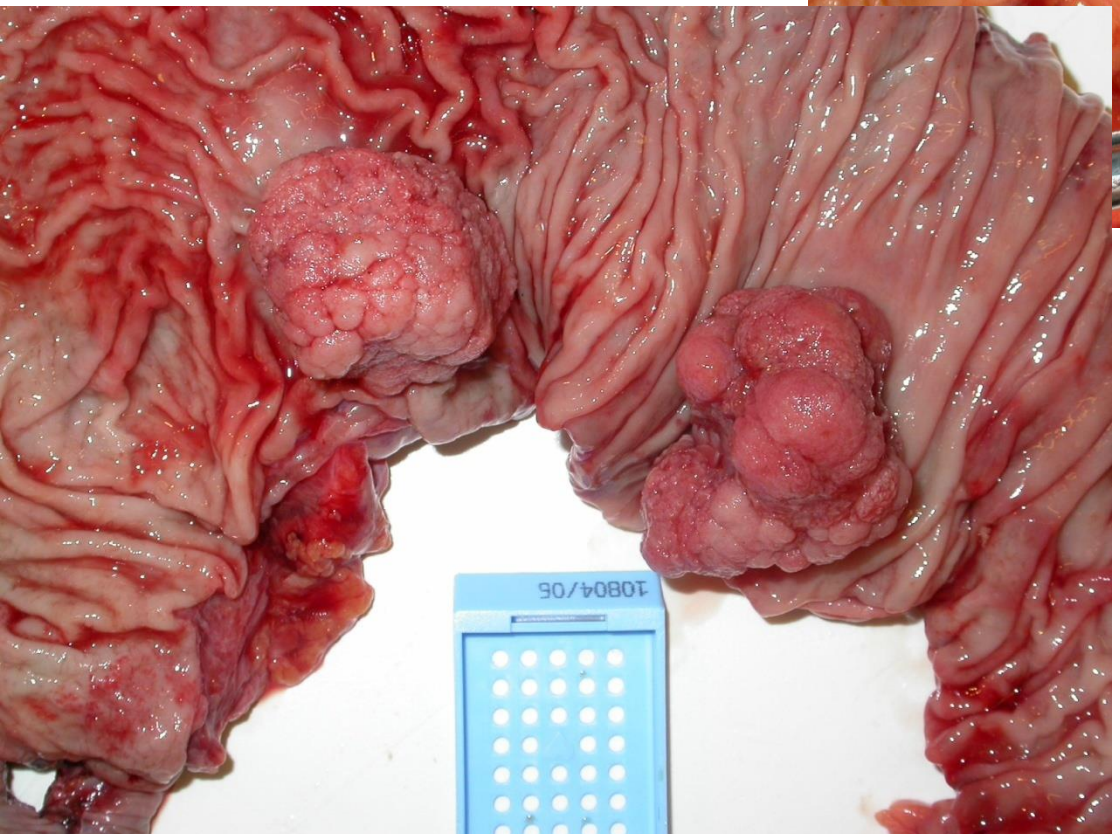
Adenoma tubulare

Polyps



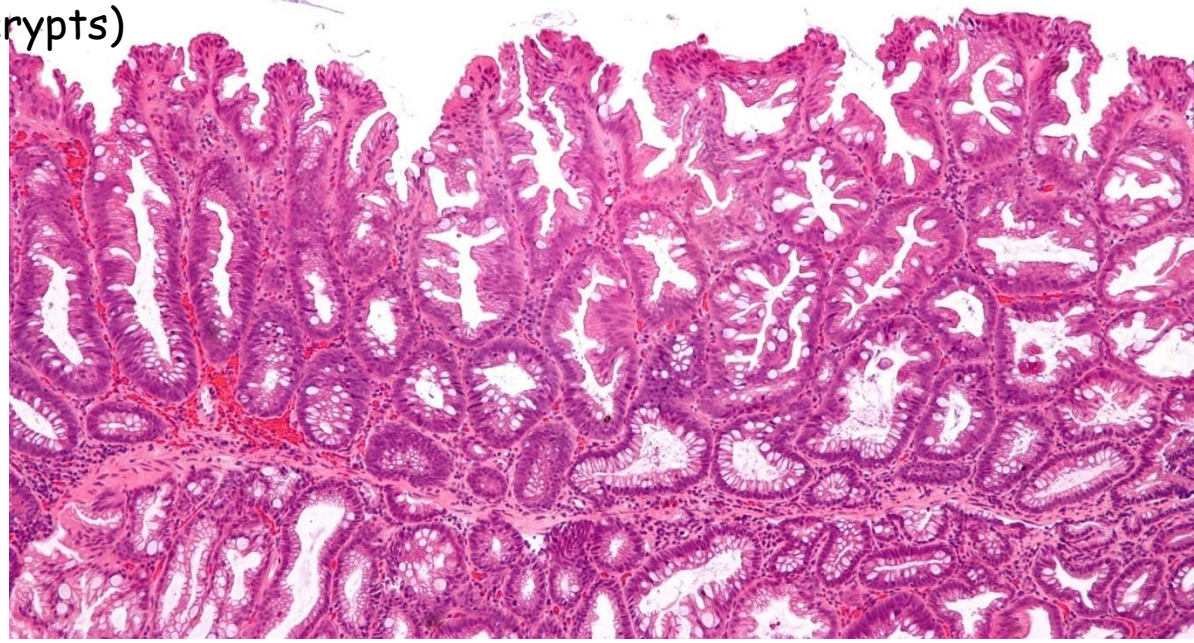
Polyps





NEOPLASTIC POLYPS- ADENOMAS II.

- **SESSILE SERRATED ADENOMA**
  - Right colon
  - Resemble Hyperplastic polyps (but serrated morphology –not only at the surface- at the crypt base too,with lateral growth and dilated crypts)
  - **NO DYSPLASIA**
  - **MALIGNANT POTENTIAL**

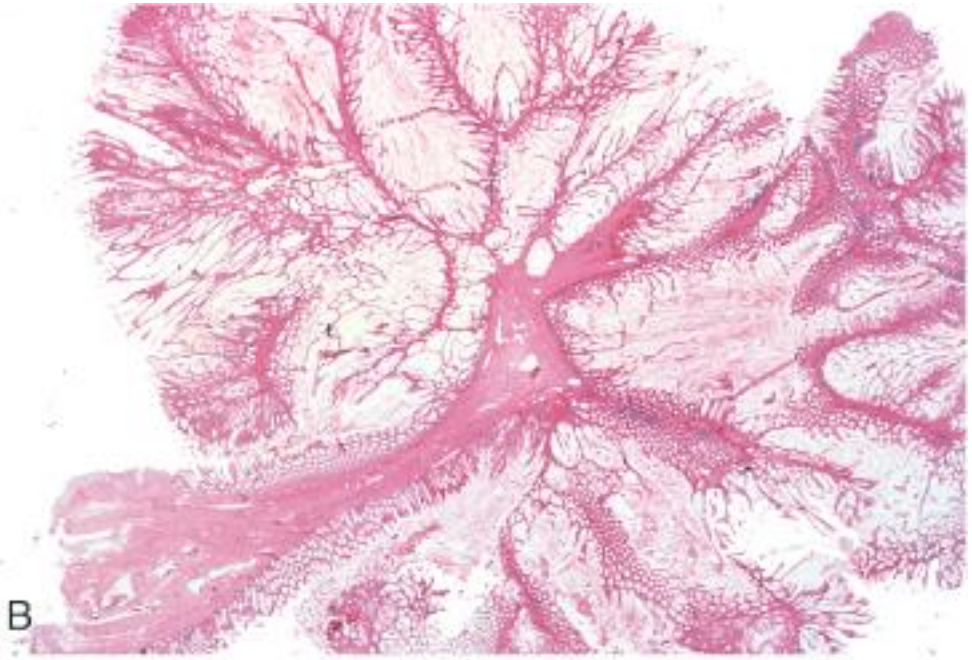


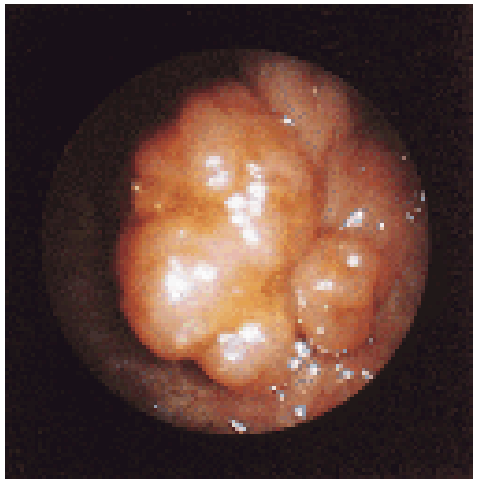
http://commons.wikimedia.org/wiki/File:Sessile_serrated_adenoma_3_intermed_mag.jpg

POLYPOSIS SYNDROMES I.

- JUVENILE POLYPOSIS SYNDROME
  - AD
  - 3-100 polyps
  - Severe bleeding
  - Increased risk of CRC
- PEUTZ-JEGHERS SYNDROME
  - Increased pigmentation around the lips, oral mucosa,face, genitals, palms
  - GI hamartomatous polyps
  - Increased risk of CRC,pancreatic, breast, lung,ovarian and uterine cancer!

Peutz-Jeghers polyposis sy





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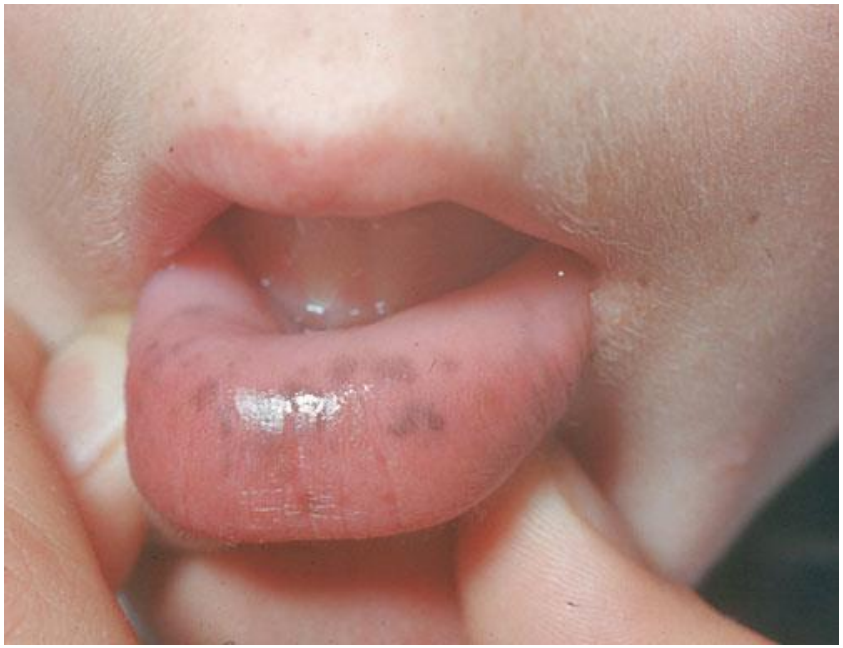


www.edu.rcsed.ac.uk/ images/709.jpg

POLYPOSIS SYNDROMES II.

- COWDEN syndrome:
  - Multiple hamartomas in GI tract and mucocutan locations
  - Increased risk of thyroid, endometrial and breast cancer

CRONKHITE-CANADA syndrome:

- Nonhereditary, of unknown cause
- 50% fatal
- >50 y
- GI hamartomatous polyps, ectodermal abnormalities

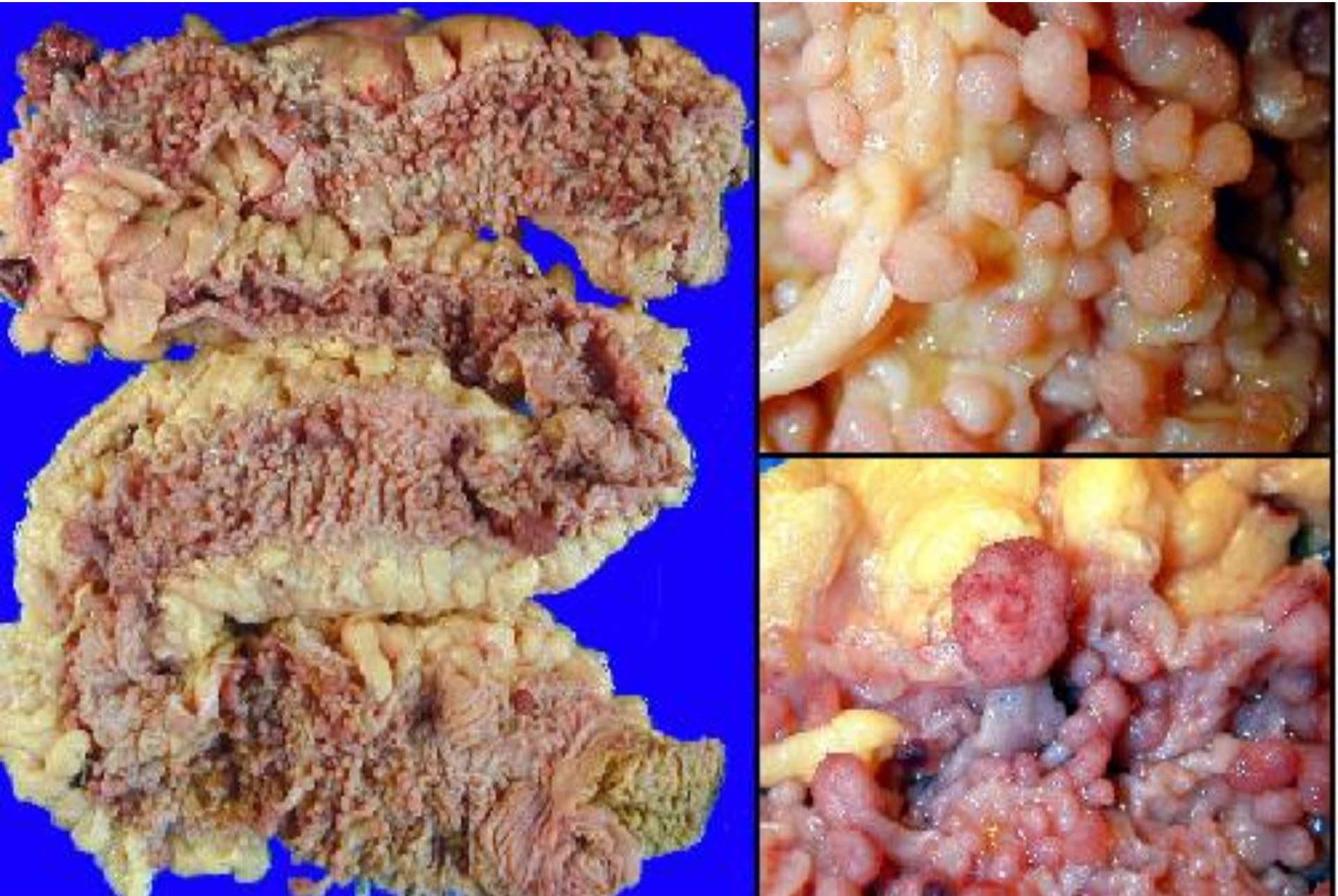
POLYPOSIS SYNDROMES III.

- **FAMILIAL ADENOMATOUS POLYPOSIS SYNDROME (FAP)**
  - **AD**
  - Increased risk of colorectal cancer!
  - Numerous adenomatous colorectal polyps with a tendency to progress to adenocarcinoma (!!!)
  - Germline mutation of the Adenomatous Polyposis Coli (APC) gene (neg regulator in the Wnt signaling pathway – β-catenin)
  - Dg criteria:
    - at least 100 polyps, APC mutation, family history of FAP
    - at least 1 of the : epidermoid cysts, osteomas, desmoid tu

POLYPOSIS SYNDROMES IV:

- FAP (Cont.)
  - increasing number of polyps with age, colorectal cc around age 40 yr
  - Extraintestinal tumors: gastric adenomas, increased incidence of hepatoblastoma, biliary tree cc
  - Extra-intestinal manifestations: desmoid tu, exostosis, dental abnormalities, congenital hypertrophy of the retinal epithelium, endocrine tu, CNS tu

Familial adenomatosus polyposis (FAP) (Kopper-Schaff:Fig.16.38)



FAP

POLYPOSIS SYNDROMES V.

- GARDNER syndrome (variant of FAP):
  - FAP+ osteomas, epidermal cysts, fibromatosis, dental abnormalities (supernumerary teeth)

- TURCOT syndrome (variant of FAP):
  - FAP + CNS tumors (medulloblastoma, glioblastoma)

GASTROINTESTINAL POLYPOSIS SYNDROMES

Syndrome	Mean Age at Presentation (yr)	Mutated Gene	Gastrointestinal Lesions	Selected Extra-Gastrointestinal Manifestations
Peutz-Jeghers syndrome	10–15	*LKB1/STK11*	Arborizing polyps; Small intestine > colon > stomach; colonic adenocarcinoma	Skin macules; increased risk of thyroid, breast, lung, pancreas, gonadal, and bladder cancers
Juvenile polyposis	<5	*SMAD4, BMPR1A*	Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma	Pulmonary arteriovenous malformations, digital clubbing
Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome	<15	*PTEN*	Hamartomatous polyps, lipomas, ganglioneuromas, inflammatory polyps, risk of colon cancer	Benign skin tumors, benign and malignant thyroid and breast lesions
Cronkhite-Canada syndrome	>50	Nonhereditary	Hamartomatous colon polyps, crypt dilatation and edema in nonpolypoid mucosa	Nail atrophy, hair loss, abnormal skin pigmentation, cachexia, and anemia

GASTROINTESTINAL POLYPOSIS SYNDROMES (Cont.)

Syndrome	Mean Age at Presentation (yr)	Mutated Gene	Gastrointestinal Lesions	Selected Extra-Gastrointestinal Manifestations
Tuberous sclerosis		*TSC1, TSC2*	Hamartomatous polyps (rectal)	Facial angiofibroma, cortical tubers, renal angiomyolipoma
Classic FAP	10–15	*APC, MUTYH*	Multiple adenomas	Congenital RPE hypertrophy
Attenuated FAP	40–50	*APC, MUTYH*	Multiple adenomas	
Gardner syndrome	10–15	*APC, MUTYH*	Multiple adenomas	Osteomas, desmoids, skin cysts
Turcot syndrome	10–15	*APC, MUTYH*	Multiple adenomas	CNS tumors, medulloblastoma

LYNCH SYNDROME (Hereditary non-polyposis colorectal cancer -HNPCC)

- increased risk of developing right colon cancer,endometrium,stomach,ovary, ureter, brain tumors etc.
- Microsatellite instability due to defective mismatch repair (**germline mutations in mismatch repair genes**)
- Five **mismatch repair genes may be** mutated: MSH2, MLH1, PMS1, PMS2, MSH6

LYNCH SYNDROME

- **Amsterdam criteria**
  - At least 3 family members affected by cancer (colorectal, endometrium, small bowel, ureter, renal pelvis)
  - The patient is a close relative of the other two
  - The cancer manifests at least in two consecutive generations
  - At least one cancer occurs before the age of 50
  - FAP may be excluded
  - Cancers were diagnosed histologically

- Muir-Torre syndrome: HNPCC+sebaceous gland tu
- Turcot syndrome: HNPCC+ CNS tu

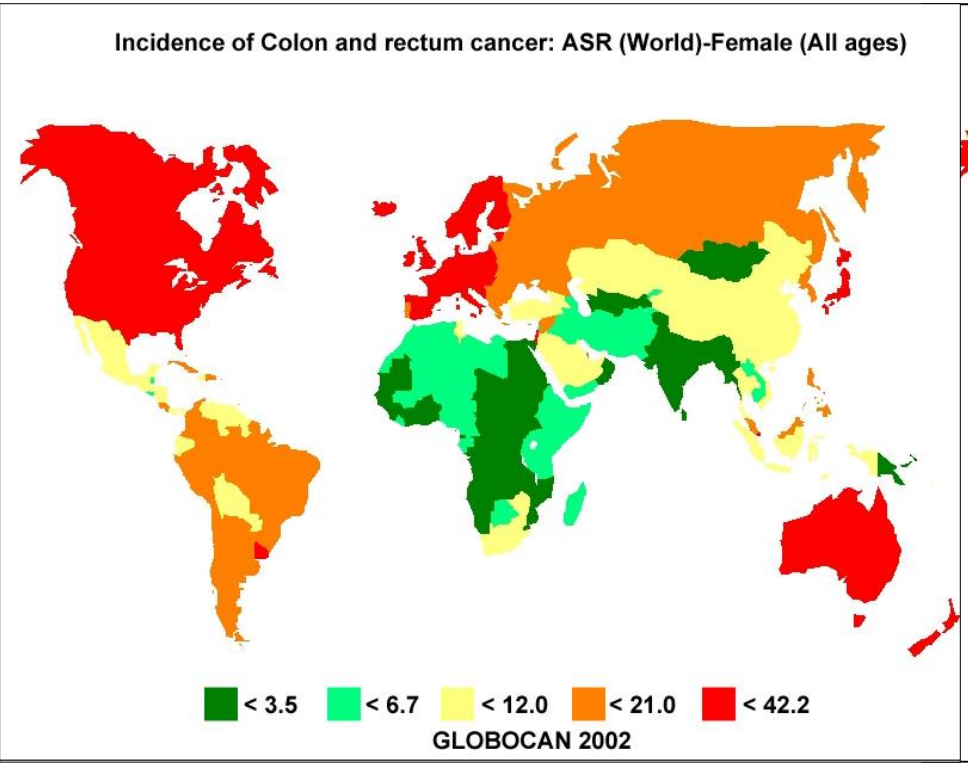
Familial and Sporadic Colon Neoplasia- Features

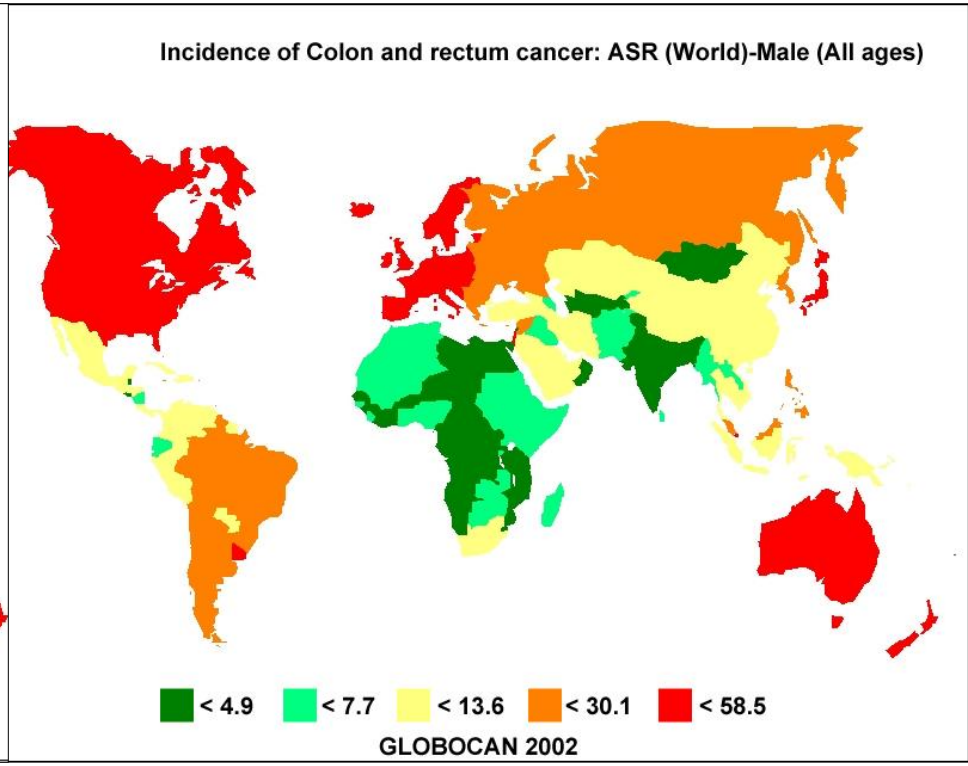
Etiology	Molecular Defect	Target Gene(s)	Transmission	Predominant Site(s)	Histology
Familial adenomatous polyposis (70% of FAP)	APC/WNT pathway	*APC*	Autosomal dominant	None	Tubular, villous; typical adenocarcinoma
Familial adenomatous polyposis (<10% of FAP)	DNA mismatch repair	*MUTYH*	None, recessive	None	Sessile serrated adenoma; mucinous adenocarcinoma
Lynch sy	DNA mismatch repair	*MSH2, MLH1*	Autosomal	Right side	Sessile serrated adenoma; mucinous adenocarcinoma
Sporadic colon cancer (80%)	APC/WNT pathway	*APC*	None	Left side	Tubular, villous; typical adenocarcinoma
Sporadic colon cancer (10% to 15%)	DNA mismatch repair	*MSH2, MLH1*	None	Right side	Sessile serrated adenoma; mucinous adenocarcinoma

COLORECTAL ADENOCARCINOMA

- The most common malignant tumor of the GI tract
- 2nd cancer related death (after lung cc)

COLORECTAL CARCINOMA INCIDENCE





www.cancerresearch.org.au/images/colon_cancer

Sporadic (non familial) colorectal cancer Epidemiology

- 25-55 / 100 000 in Europe
- More common in males
- Meat, smoking, alcohol
- NSAIDs-protective role
- Ulcerative colitis (up to x20 incidence)
- Previous irradiation to the pelvis
- Most common: rectum – sigmoid

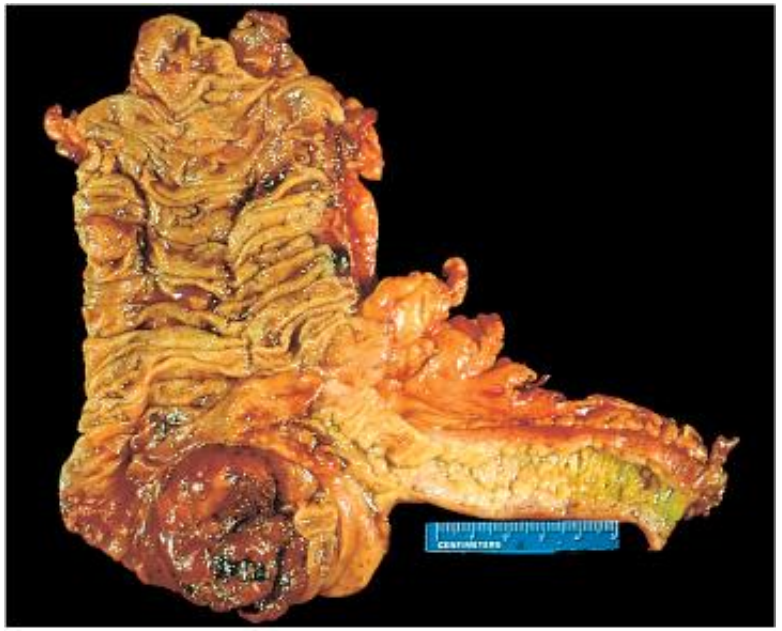
  (Rectum 15%, sigmoid 20%, left colon 10%, transversum 12%, right colon 8%, cecum 8%)

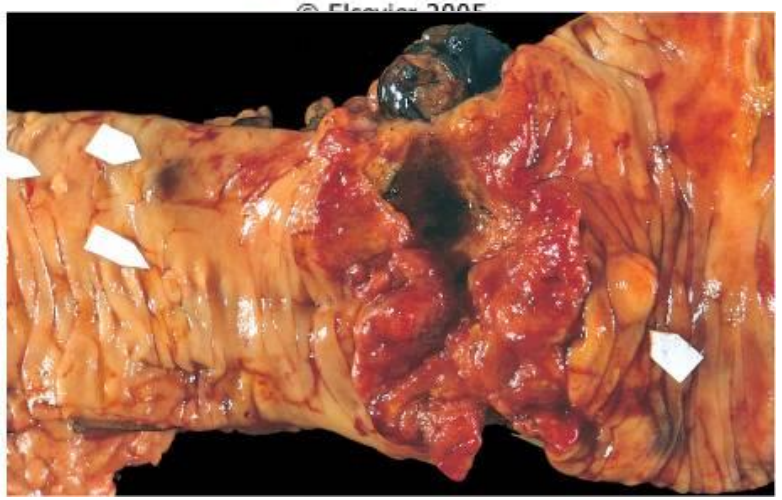
CRC- Symptoms

- **No symptoms**
- Haematochesia
- **Iron deficiency anaemia**
- Changes in bowel habits
- Abdominal discomfort
- Tenesmus
- Fever, malaise, weight loss, pain
- Ileus
- Acute abdomen due to perforation

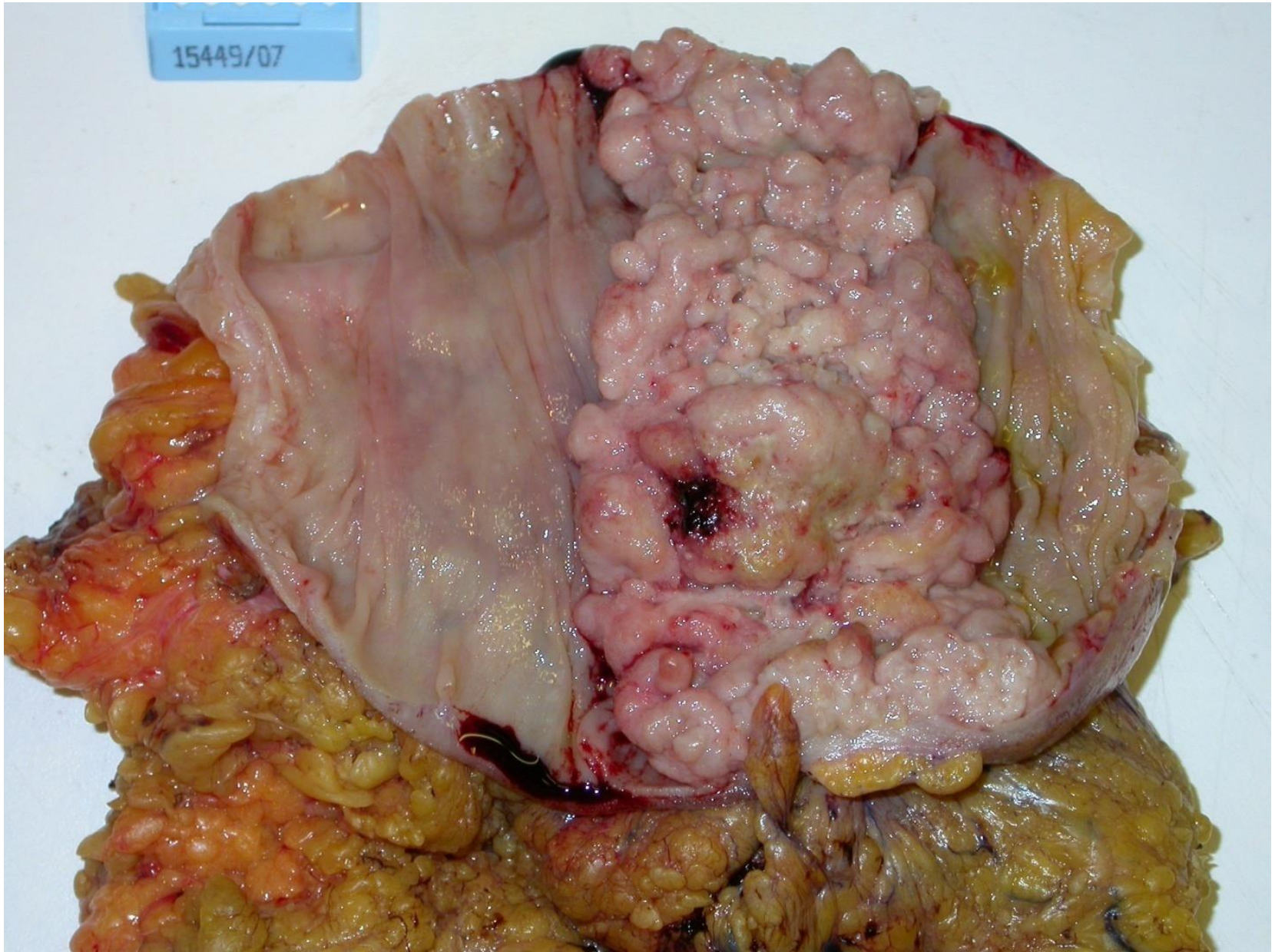
CRC- Macroscopy

- Exophytic
  - Mainly cancers of the right colon
- Excavated/ulcerative
  - Mainly transversum, left colon
  - Napkin- ring constriction, obstruction
- Diffusely infiltrating

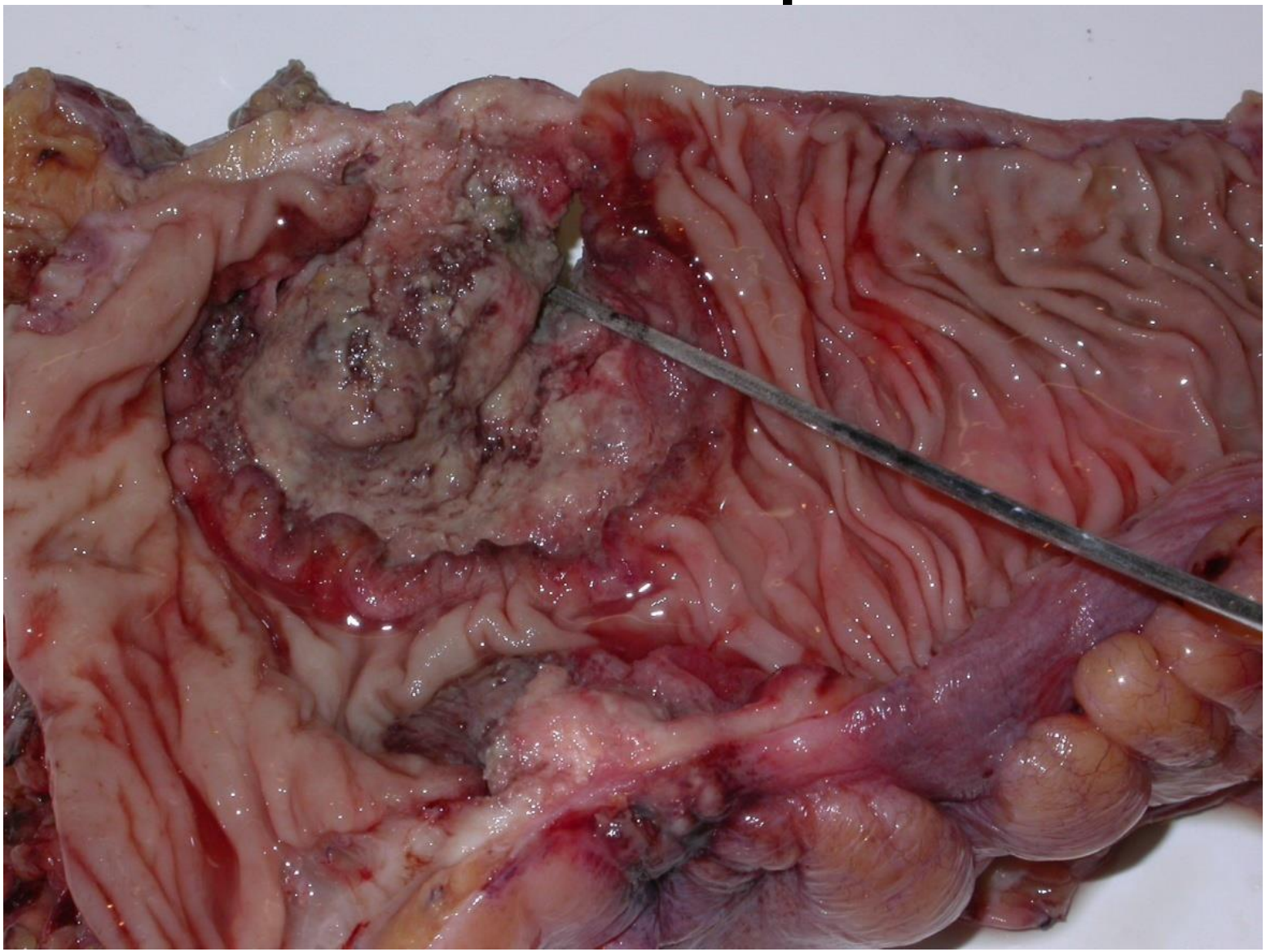




Adenocarcinoma

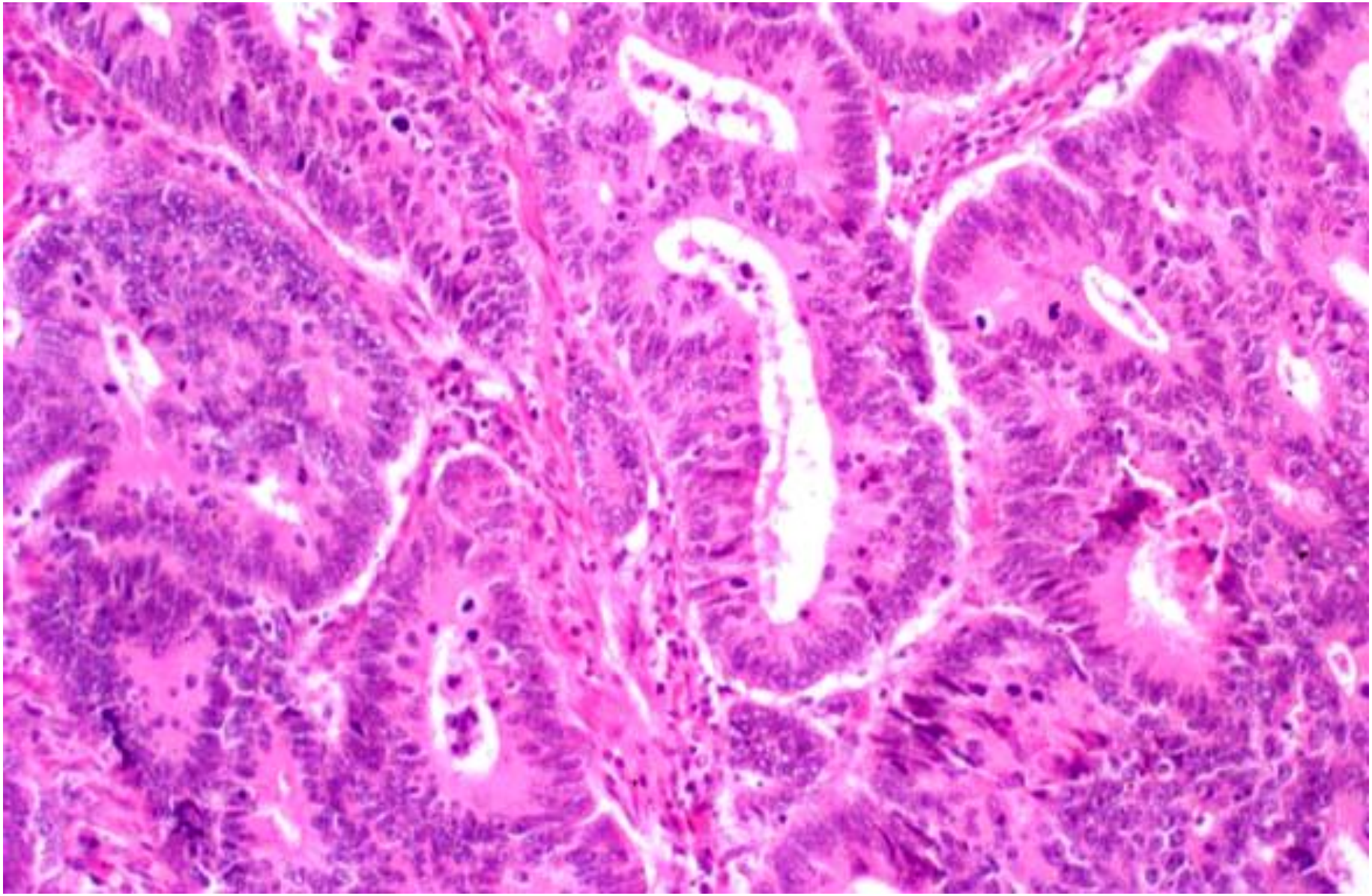


Adenocarcinoma- perforation

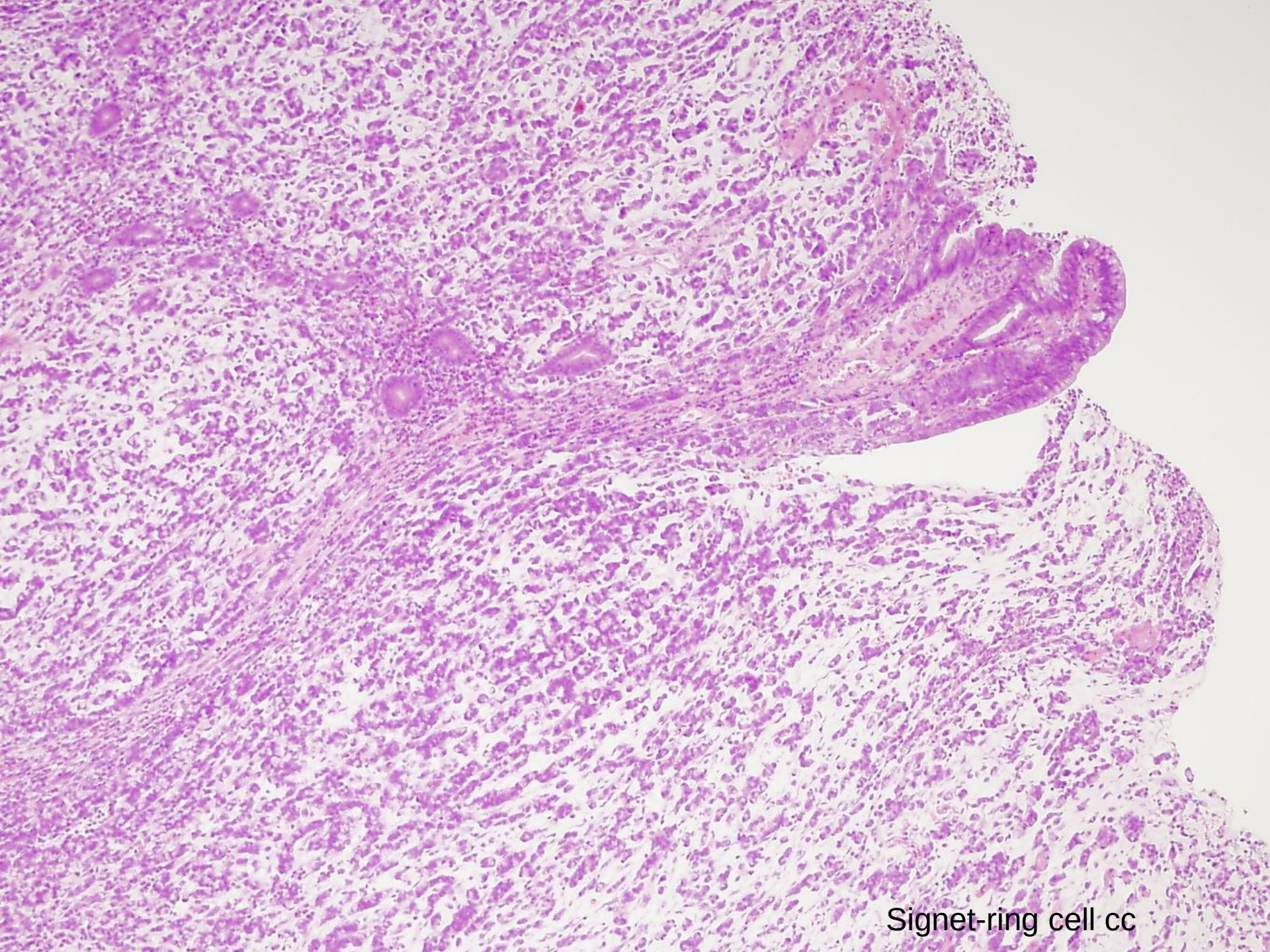


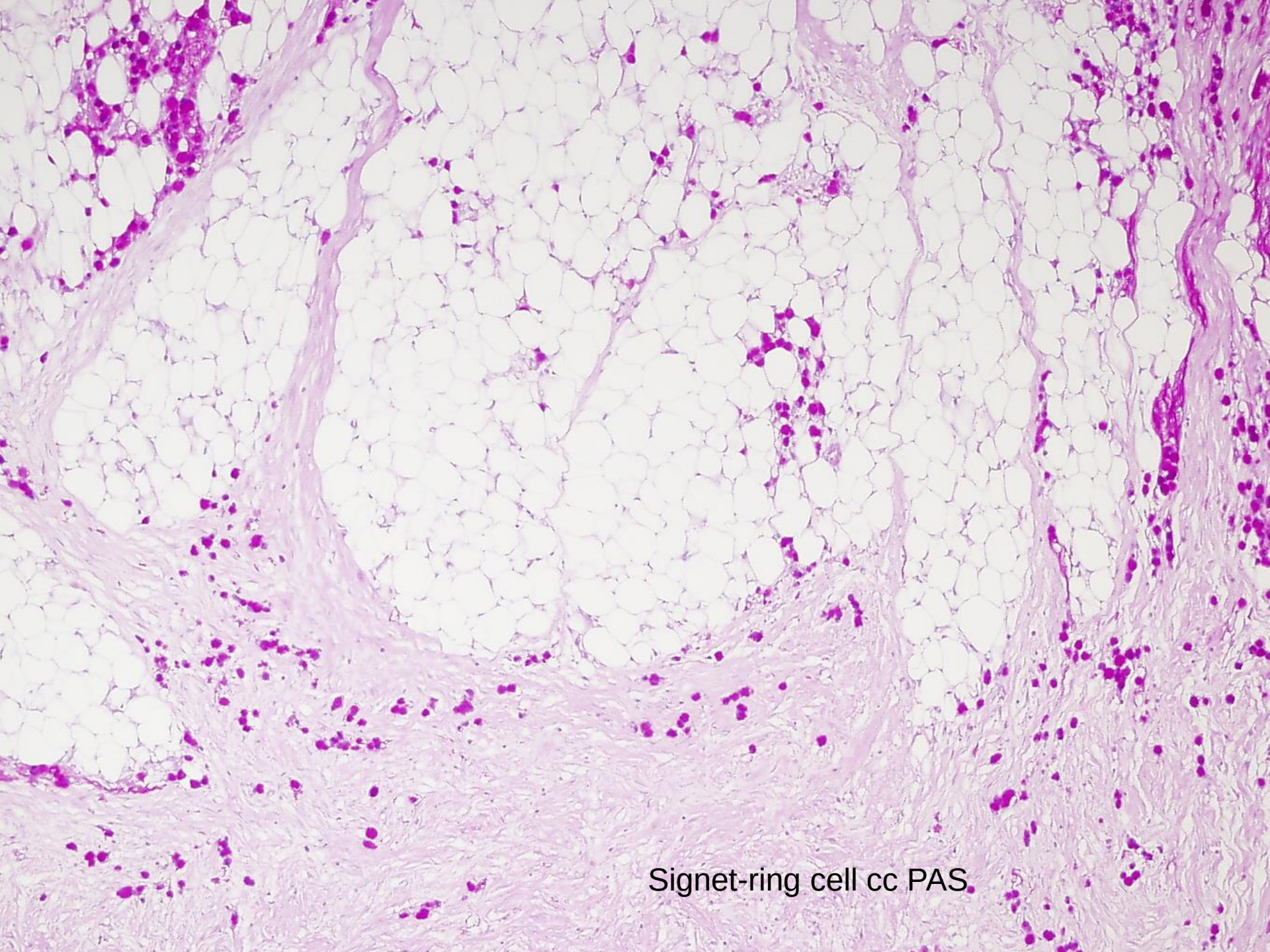
Histological types

- Adenocarcinoma
- Mucinous adenocarcinoma
- Signet-ring cell carcinoma
- Adenosquamous carcinoma
- Squamous cell carcinoma (anal)
- Medullary carcinoma
- Undifferentiated carcinoma



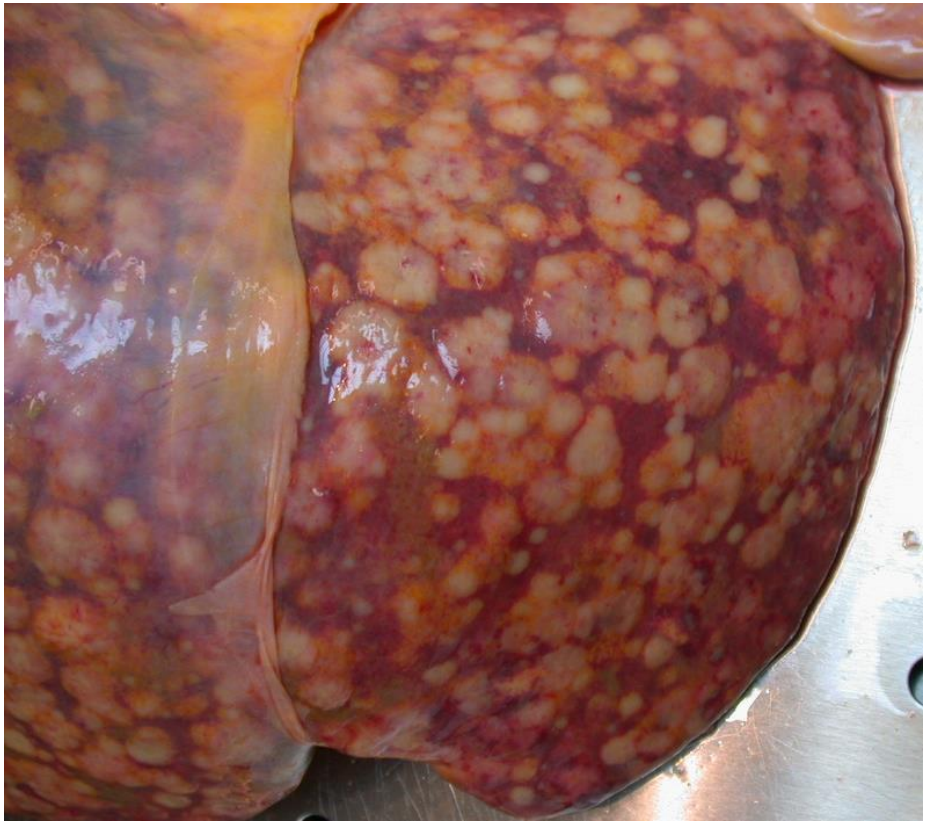
Adenocarcinoma G2


Signet-ring cell cc

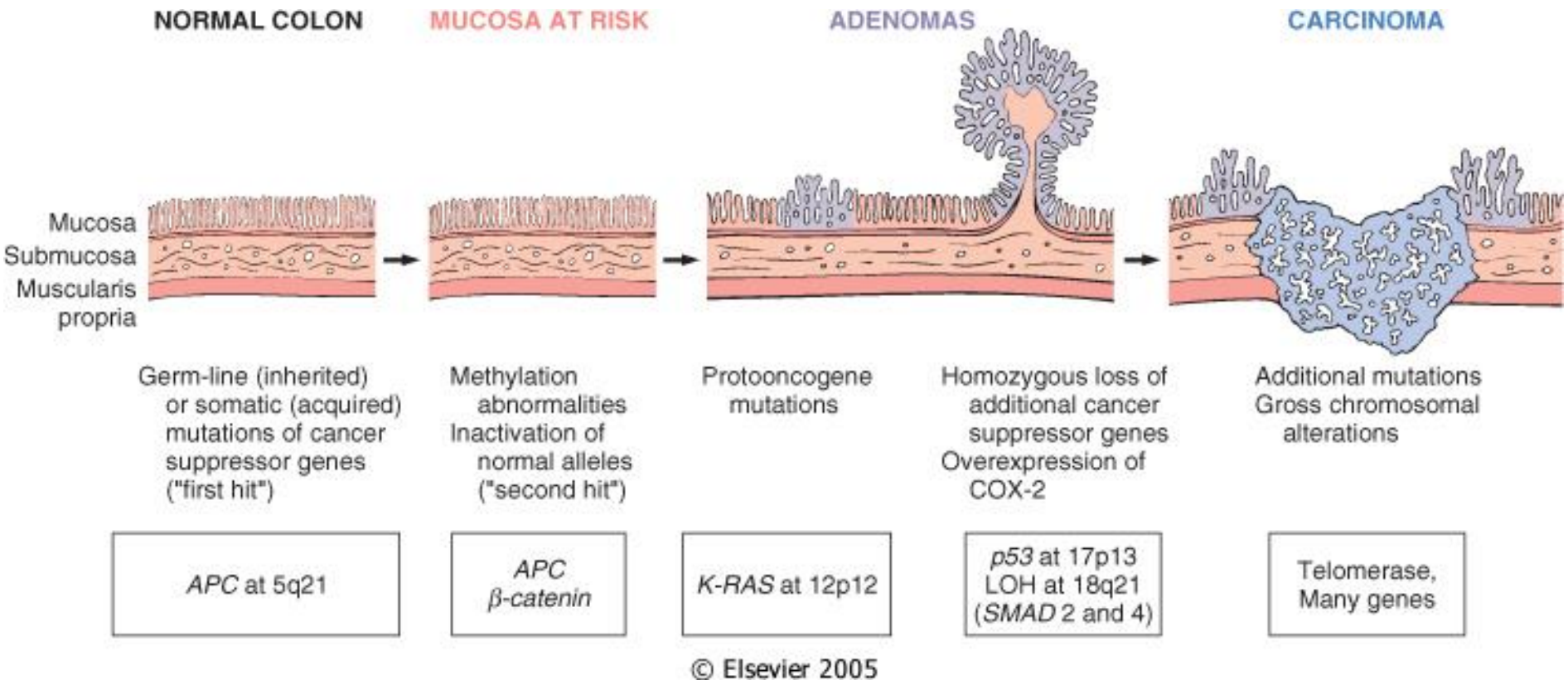

Signet-ring cell cc PAS

Spread

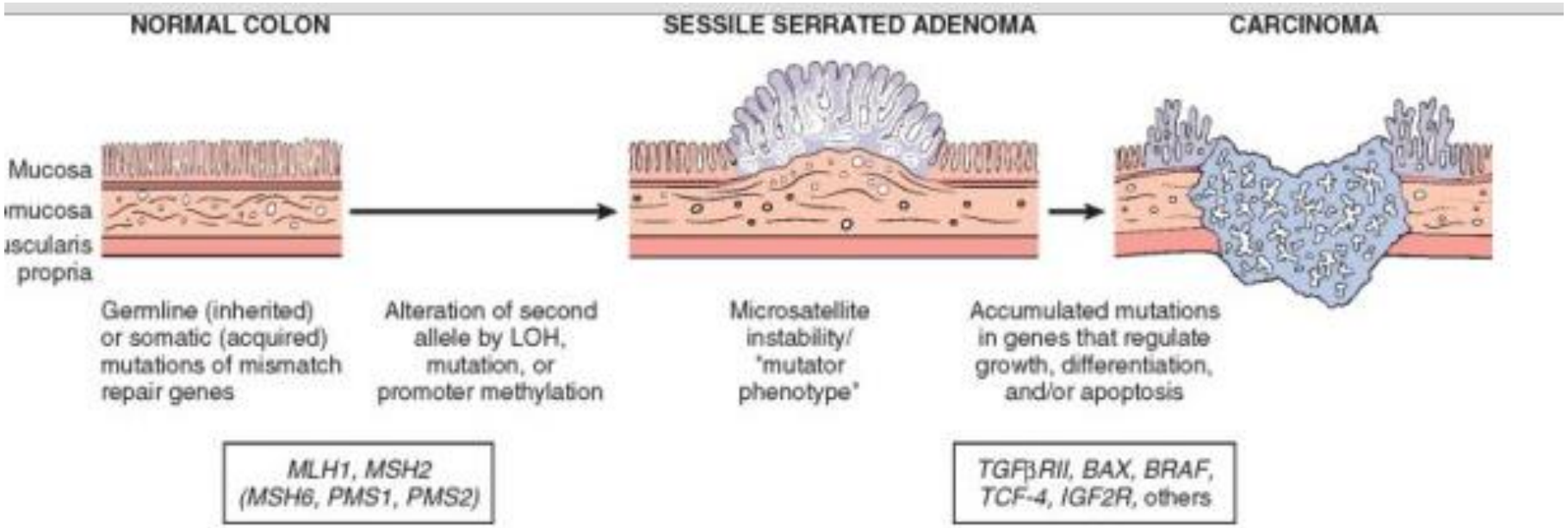
- Local spread
- Peritoneum, organs in the vicinity
- Lymphatics
  - Regional lymph nodes
- Vena portae
  - LIVER
- Vena cava inferior (lower third of the rectum)
  - Lung



Adenoma → carcinoma

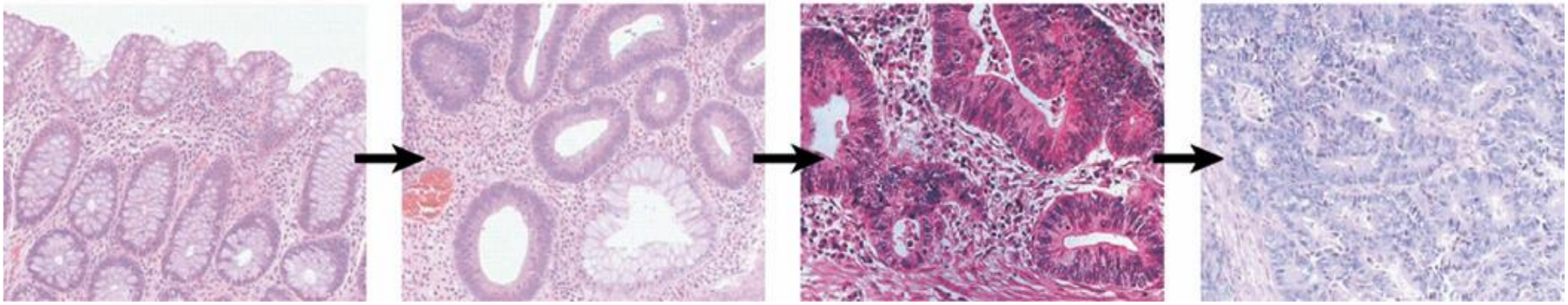


Adenoma → carcinoma

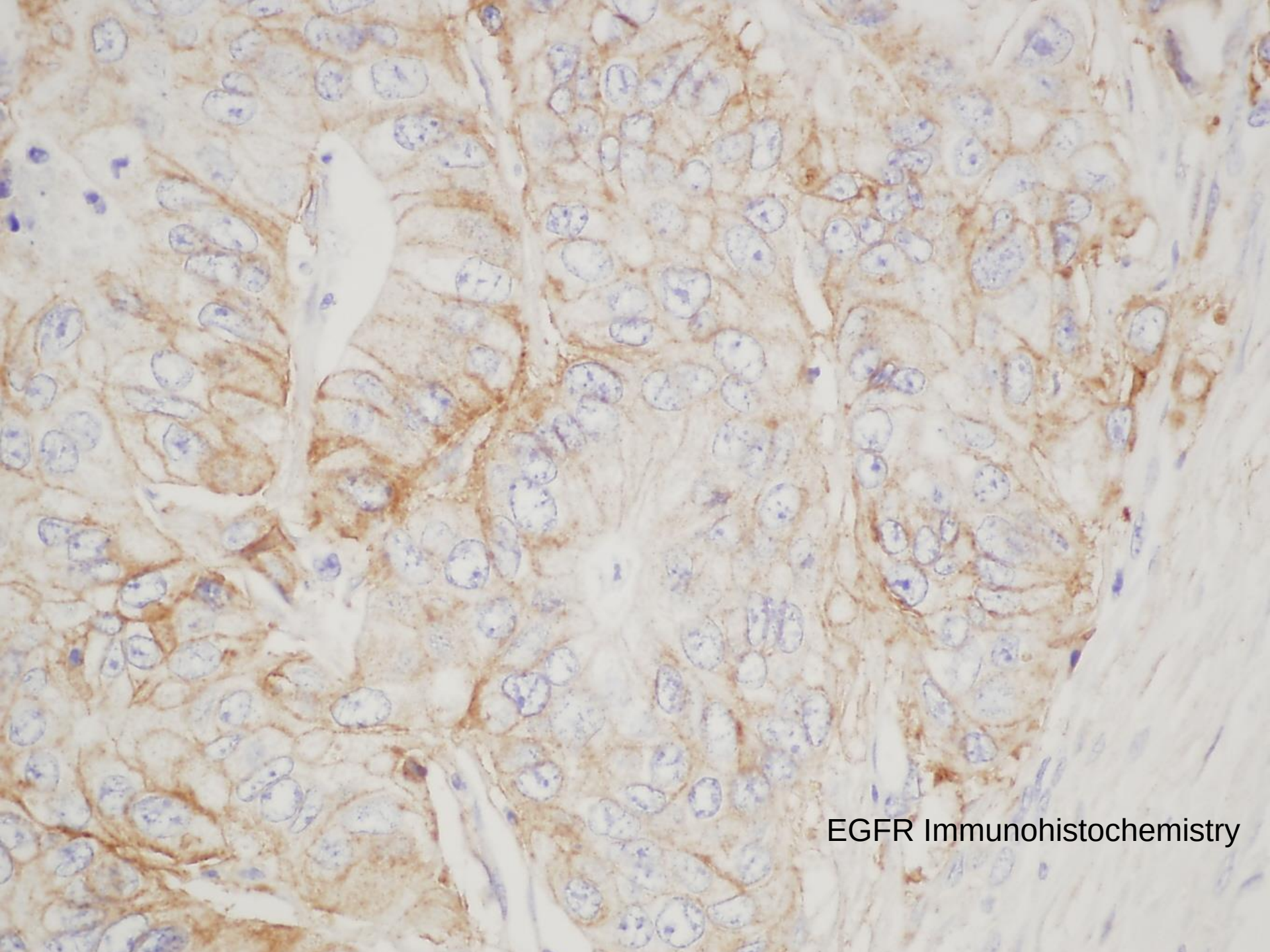


Colorectal cancer progression
in sporadic and high risk genetic syndromes

Normal colonocyte	Tumor initiation	Tumor progression	Carcinoma
Sporadic →	Normal (30-50 years) →	Normal (10-20 years) →	6% risk (mean age ~ 68 years)
FAP →	Accelerated (5-20 years) →	Normal →	100% risk (mean age ~ 40 years)
Lynch →	Normal →	Accelerated (1-3 years) →	up to 80% risk (mean age ~ 40 years)



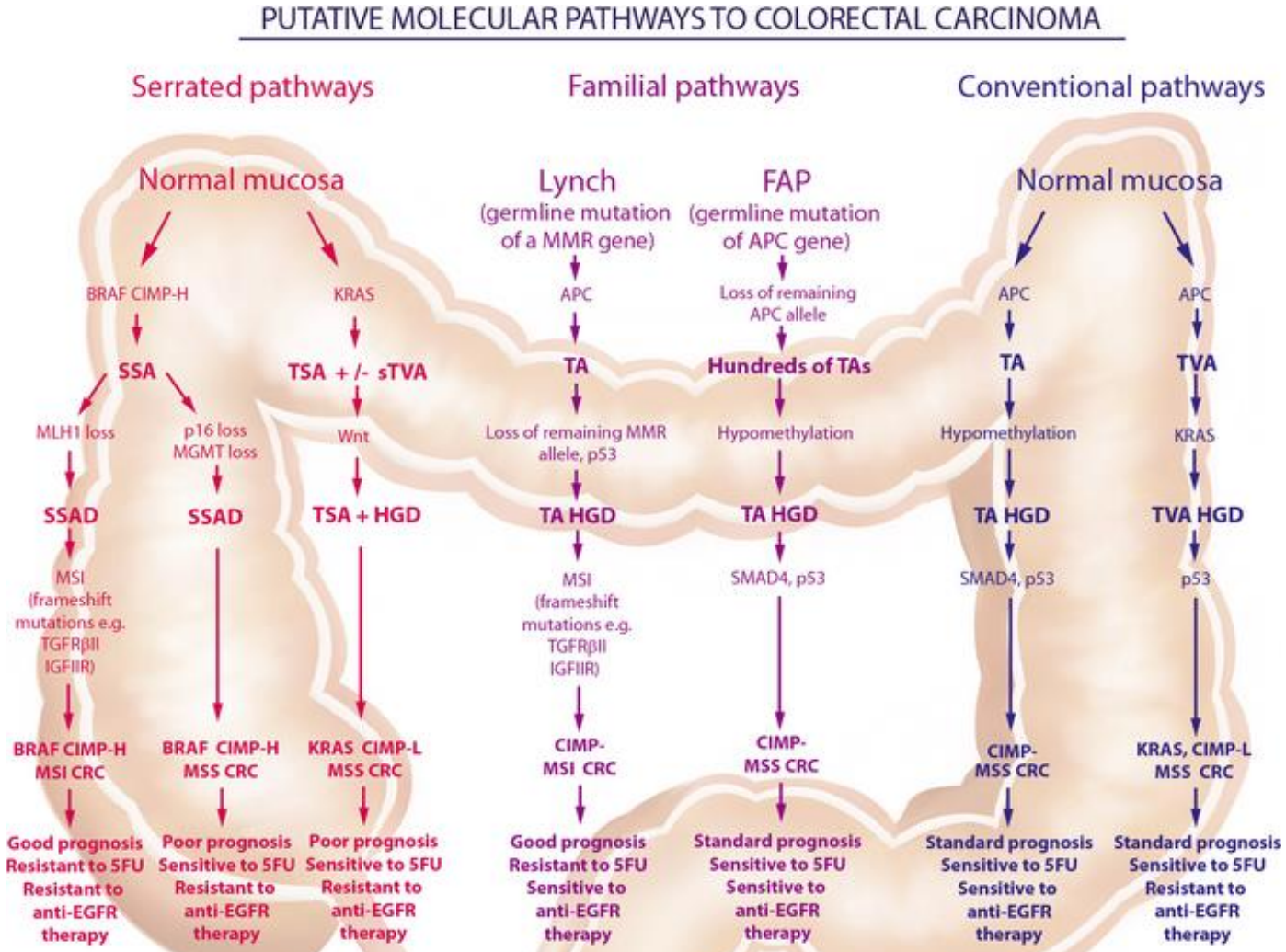
Grady W.M., Carthers J.M. Reviews in basic and clinical gastroenterology
Gastroenterology 2008 135:1078-1099


EGFR Immunohistochemistry

EGFR and RAS/RAF activation in CRC

- Increased EGFR expression.
  - The gene is usually not mutated, but increased copy number occurs. This is the base of anti-EGFR therapy (cetuximab), but….
- Mutations (K-RAS) activating the RAS/RAF signaling pathway
  - are also predictive and prognostic indicators in CRC patients, being inversely correlated with response to anti-EGFR mABs (Benvenuti et al.CancerRes 2007.)
- Identification of patients who are likely to respond to anti-EGFR treatment
  - („wild" type K-RAS) is important.

The serrated pathway to colorectal carcinoma: current concepts and challenges



Histopathology
Volume 62, Issue 3, pages 367-386, 22 JAN 2013 DOI: 10.1111/his.12055
http://onlinelibrary.wiley.com/doi/10.1111/his.12055/full#his12055-fig-0011

Other neoplasms

- NET/NEC (see small bowel)
- Mesenchymal tumors
  - GIST (see small bowel)
- Lymphomas
- Metastatic tumors
  - Breast cc, lung cc, Malignant melanoma

PERITONEUM

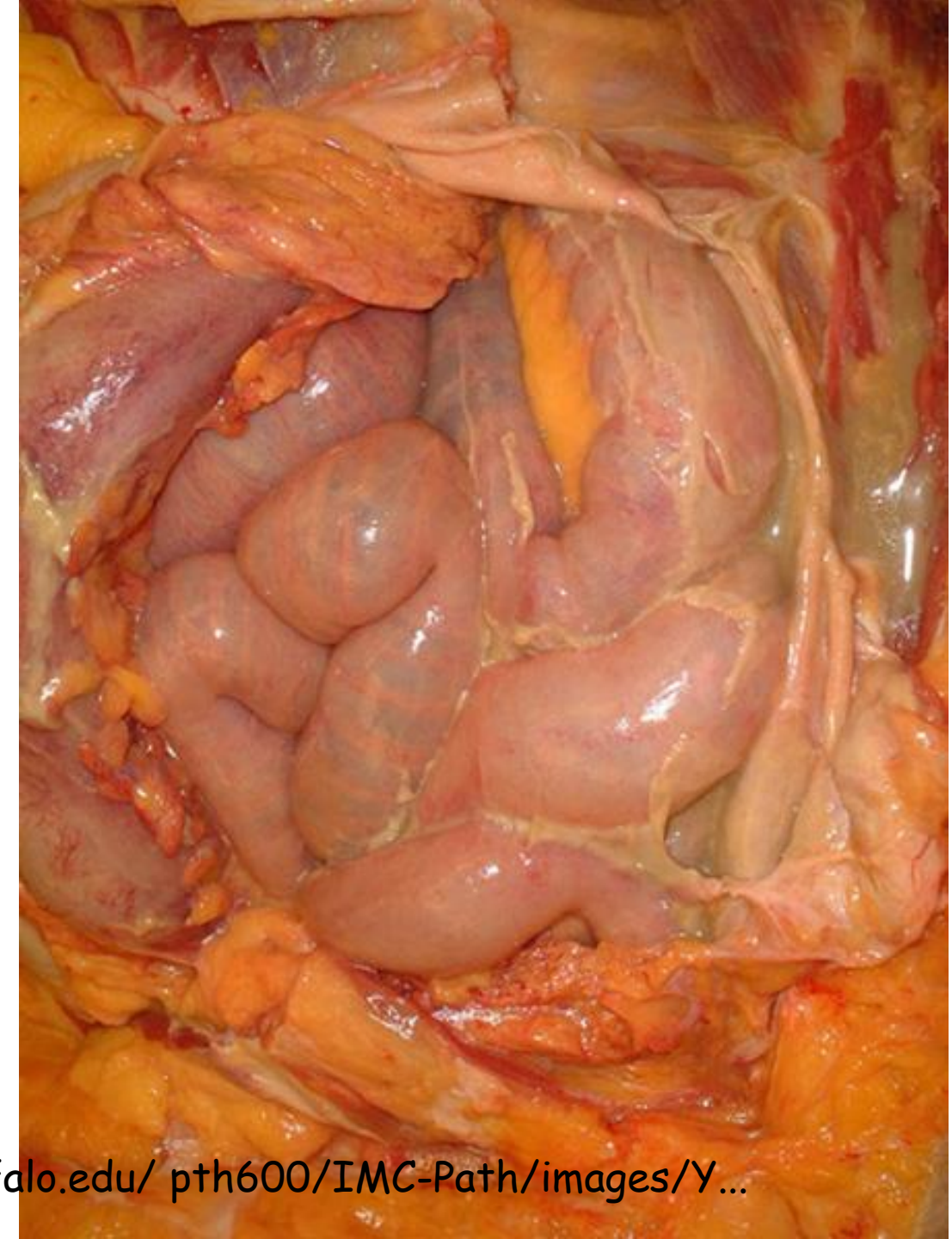
PERITONEUM

- Peritonitis
  - Sterile: bile, pancreatic juice, surgery (talcum, foreign body), autoimmune (SLE), pelvic inflammations, endometriosis
  - Infectious:
    - bacterial: perforation, pathogenic agents penetrating the bowel wall, trauma, gynaecological diseases (Gonococcus, Chlamydia), spontaneous peritonitis (liver cirrhosis)

Peritonitis: morphology

- Acute
- Chronic

- Granulomatous (tbc, foreign material)
- Reactive peritoneal fibrosis (postoperative)
- Sclerosing peritonitis (primary or secondary)



www.smbs.buffalo.edu/ pth600/IMC-Path/images/Y...

Primary tumors

- Mesothelioma
  - Benign
  - Malignant
- Desmoplastic small round cell tumor

PERITONEUM: METASTATIC TUMORS

- Peritoneal carcinomatosis
  - Direct spread
  - Lymphogenic
  - Hematogenic
- Mainly metastases from GI tract and gynecological tumors