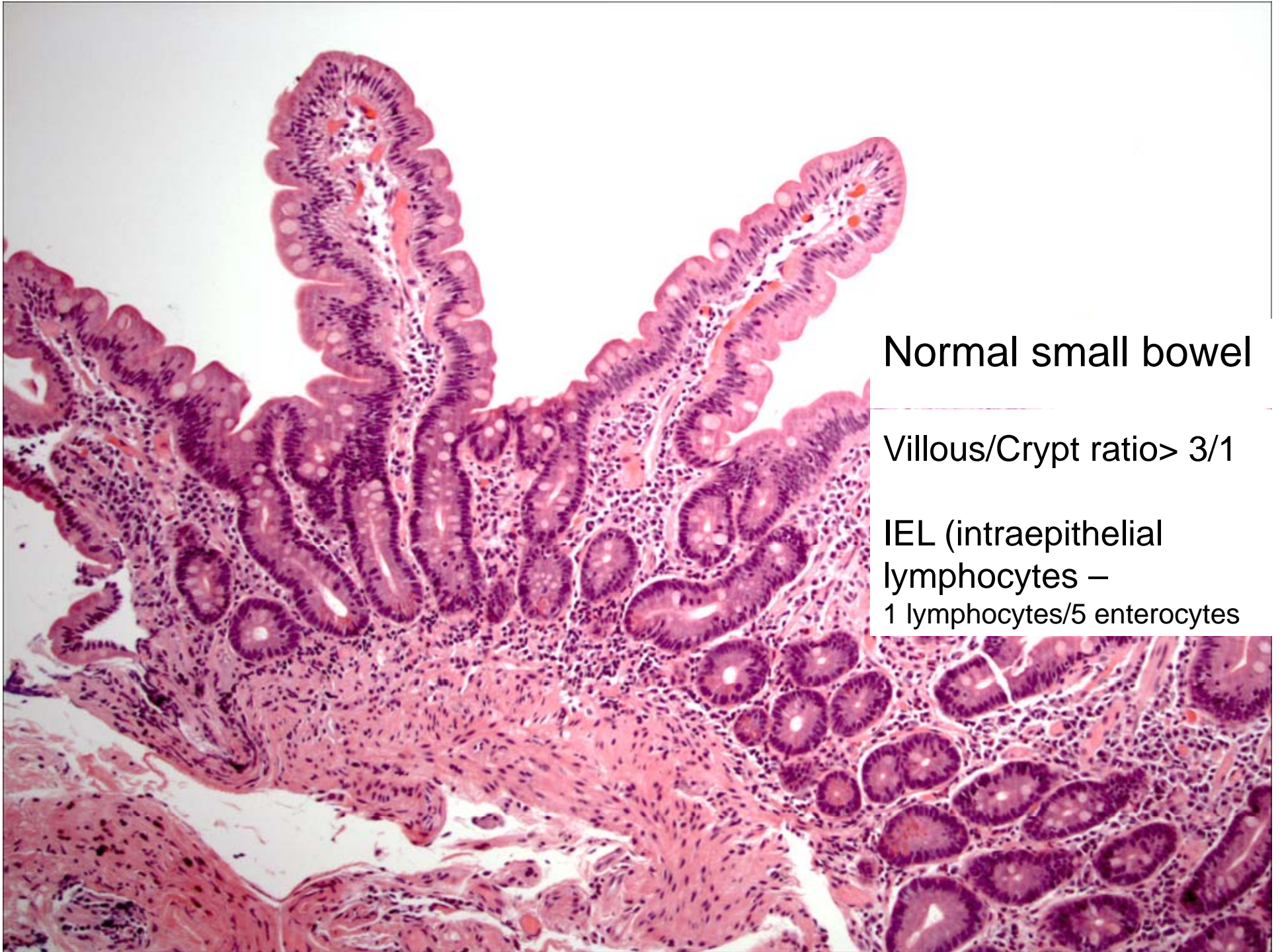


Small Intestinal Pathology

Helen Remotti, M.D.
Columbia University
Department of Pathology and
Cell Biology
her2007@columbia.edu



Normal small bowel

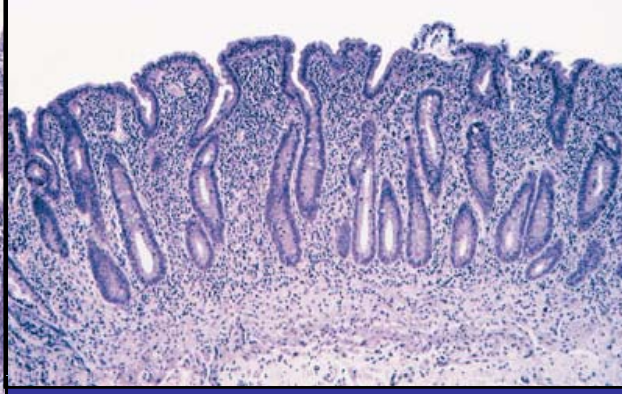
Villous/Crypt ratio $> 3/1$

IEL (intraepithelial lymphocytes –
1 lymphocytes/5 enterocytes

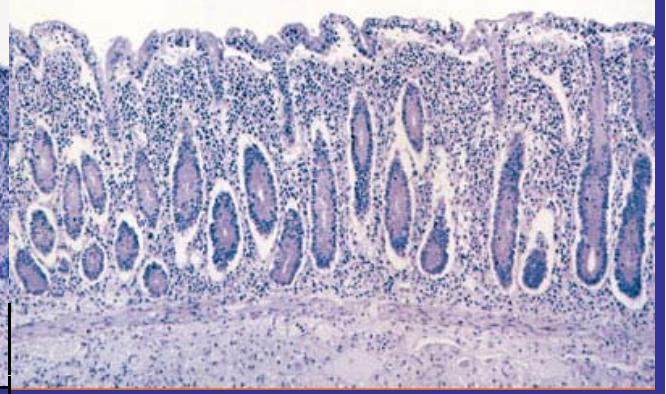
Celiac Disease



MILD
(partial villous
atrophy)



MODERATE
(subtotal villous
atrophy)



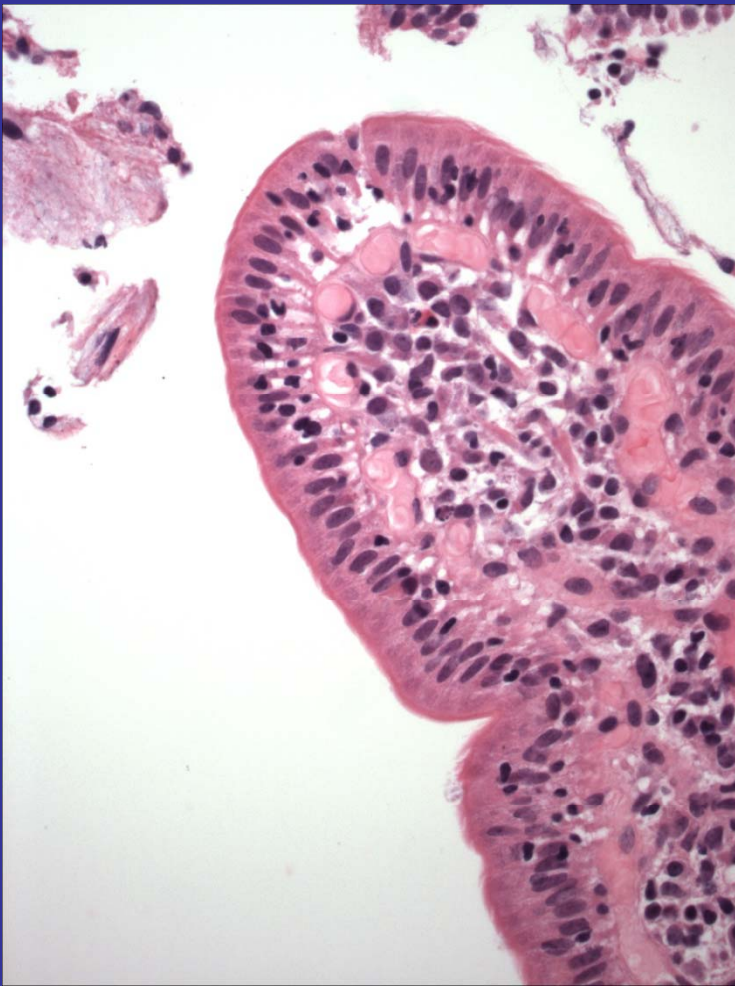
SEVERE
(total villous atrophy)

Villous atrophy – variable degree

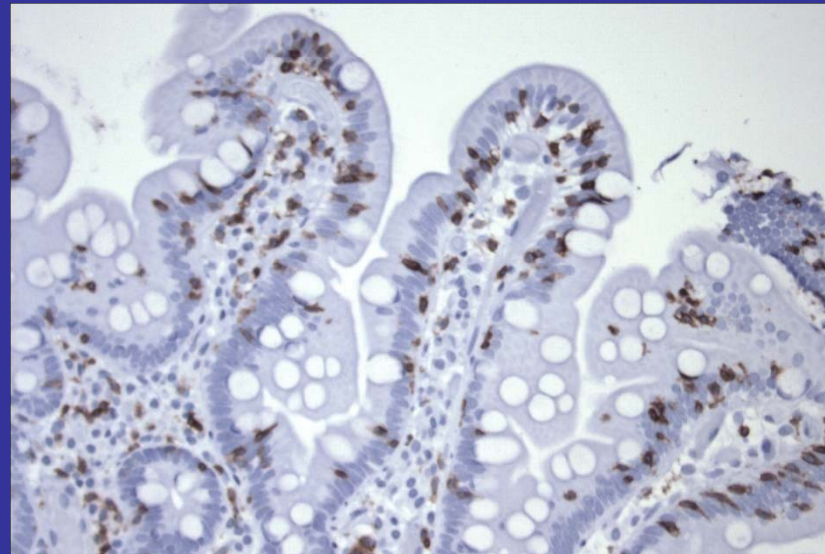
Chronic inflammation in lamina propria

Increased IELs (intraepithelial lymphocytes)

Celiac Disease— Intraepithelial lymphocytosis



IELs increased
>5 lymph/10 enterocytes
(NL: 2 lymph/10 enterocytes)

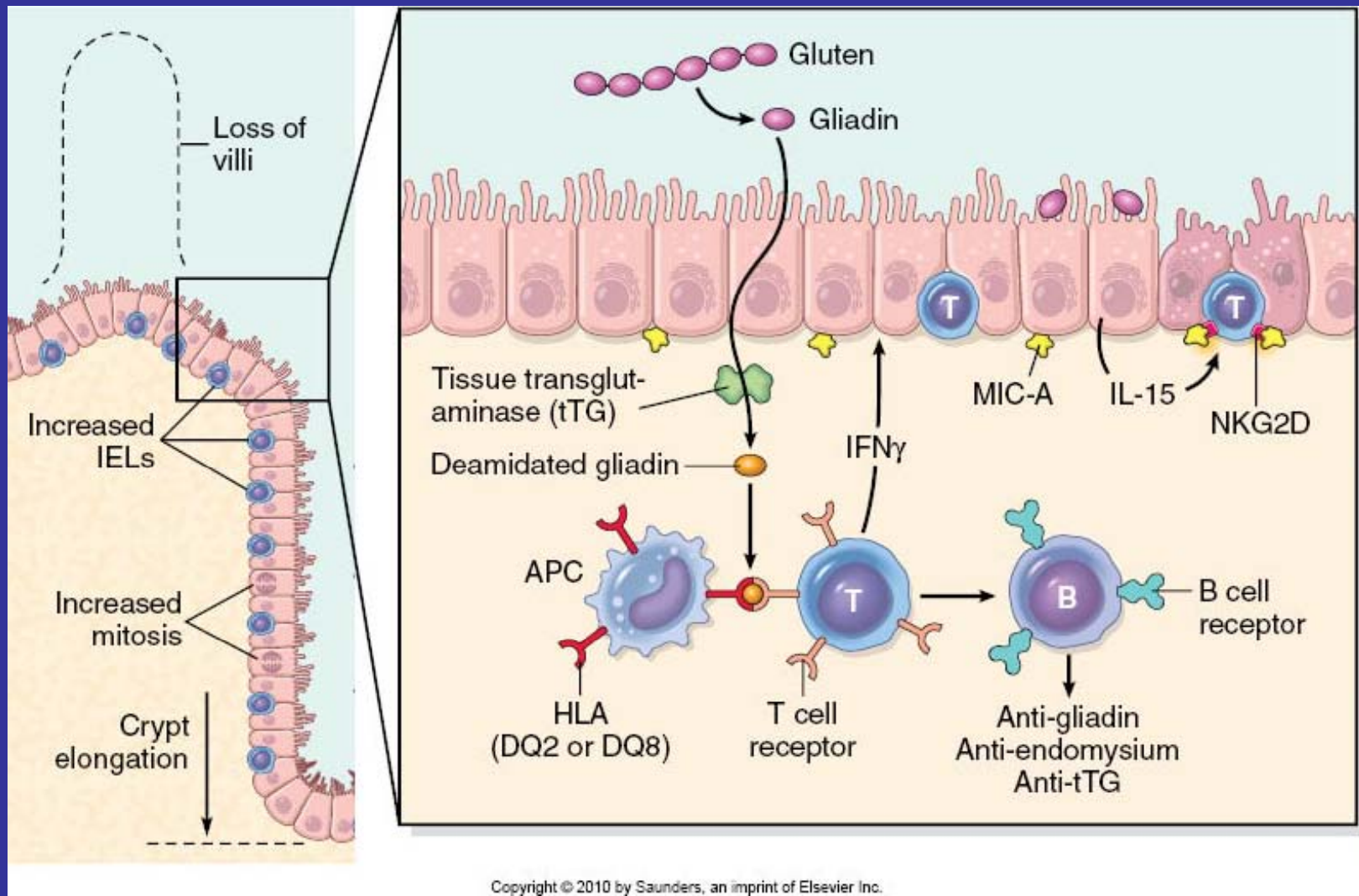


CD3 (T-cell immunostain)

Celiac Disease (CD)

- Autoimmune disease associated with wheat (gluten) ingestion.
- Sx: chronic diarrhea, abdominal pain, weight loss, iron deficiency anemia,
- Dx: autoantibodies to gliadin, tissue transglutaminase (tTG), reticulin, and endomysium.
- CD is strongly associated with HLA-DQ2 and HLA-DQ8 (however 40% of general population have at least one of these markers);

Celiac Disease - Mechanism



Conditions with histologic overlap with Celiac disease.

Increased IEL

- **H. pylori gastritis**
- Viral Gastroenteritis
- Protein intolerance
- Bacterial overgrowth
- Medications
- Autoimmune enteropathy
- Tropical sprue
- Crohn's disease

Villous blunting

- Common variable immunodeficiency
- Viral Gastroenteritis
- Protein intolerance
- Bacterial overgrowth
- Radiation/chemotherapy
- Nutritional deficiencies
- Eosinophilic gastroenteritis
- Refractory sprue
- Tropical sprue
- Crohn's disease

Celiac Disease: Diagnosis

- Documentation of malabsorption
- Demonstration of villous atrophy and/or intraepithelial lymphocytosis by small bowel biopsy
- Improvement of symptoms and mucosal histology after gluten withdrawal

Non-responsive celiac disease (NCD) (definition)

NCD- lack of initial response to gluten free diet (GFD) or recurrence of symptoms despite maintenance of (GFD)

Diagnostic approach:

- 1) re-assess initial diagnosis of CD (presence of EMA, tTG antibodies before GFD, HLA DQ2 or DQ8 status, histology).
- 2) Assess gluten free diet (50% of NCD due to dietary gluten).
- 3) Exclude other causes of diarrhea (MC, bacterial overgrowth, IBD)

Complications of CD (uncommon)

Collagenous sprue (subepithelial collagen); Lymphoma; Carcinoma



Collagenous sprue

Tropical Sprue

- Post-infectious sprue
- Enterotoxigenic bacteria (E.coli, Hemophilus)
- Response to antibiotics
- History of foreign travel: (Caribbean, Central/South America, Central/South Africa, India)
- Pathology- patchy distal and proximal small bowel; macrocytic anemia and megalocytosis due to B12 malabsorption.

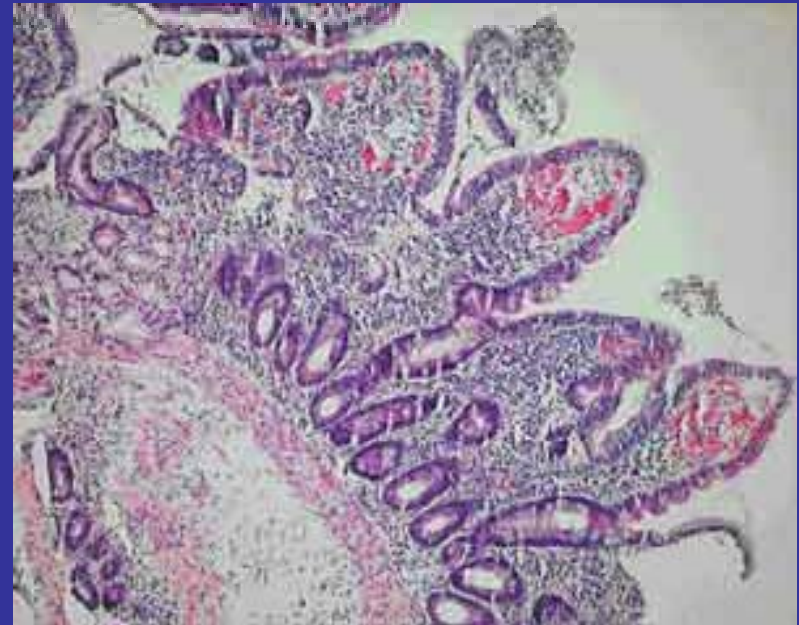
Case Study

- 62 y male from Central America had weight loss, diarrhea and macrocytic anemia.
- The blood film showed hypersegmented neutrophils and macrocytes. His serum vitamin B12 and folate levels were low.

Initial biopsy

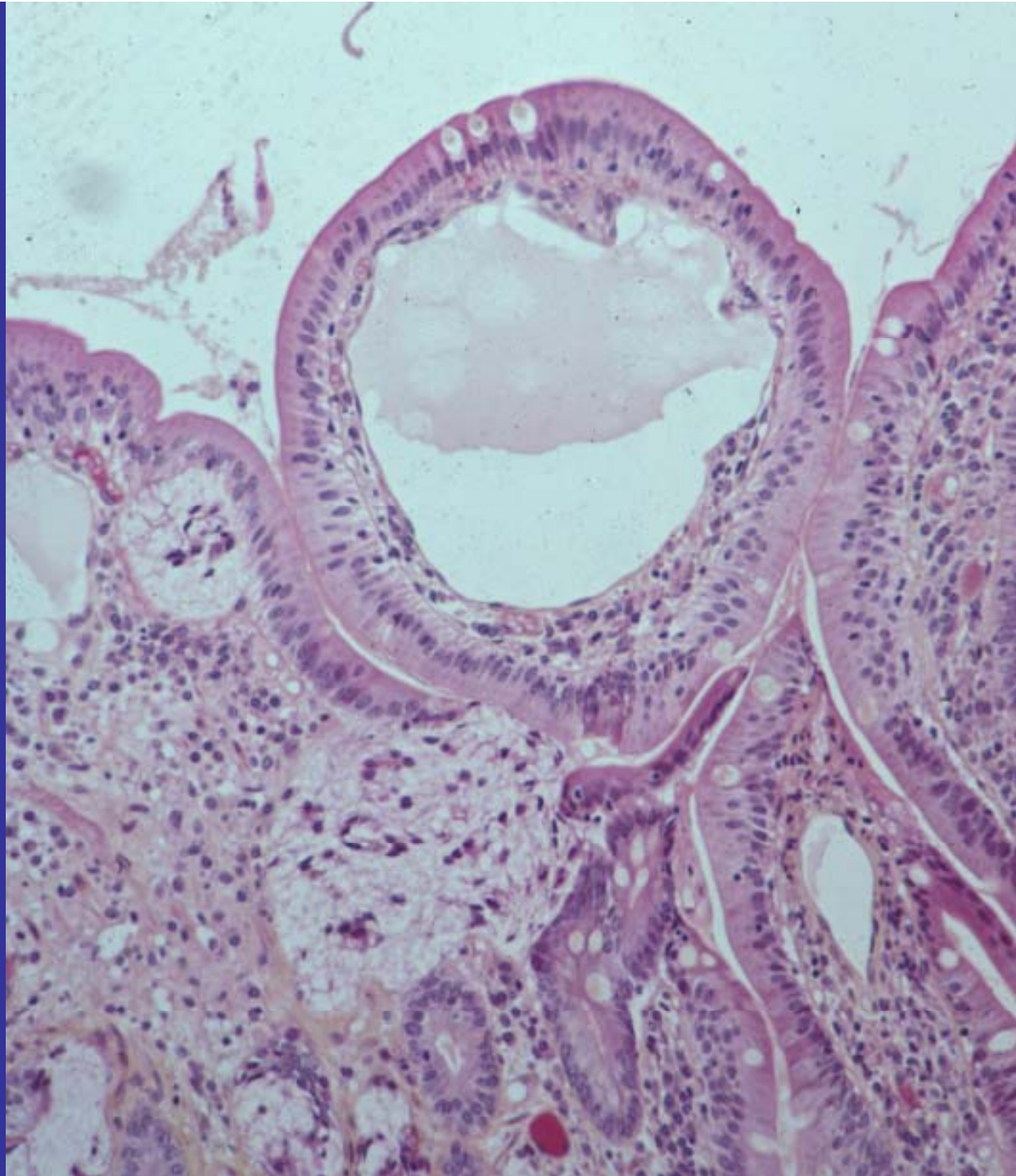


3 weeks after treatment with Doxycycline, B12 and folate.



Lymphangiectasia

- **Primary lymphangiectasia:** rare congenital disorder; defective lymphatics; normally absorbed nutrients reach the lymphatics but cannot be transported into the circulation.
- **Secondary lymphangiectasia:** more common; complication of any disorder that causes lymphatic obstruction: enlarged mesenteric lymph nodes (cancer or inflammatory), heart disease (constrictive pericarditis, CHF)



Meckel's Diverticulum

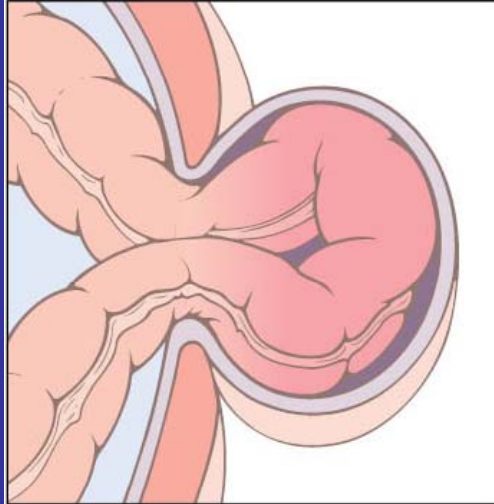
- Persistence of vitelline duct (connects gut and yolk sac)- embryologic remnant – true diverticulum (all layers of bowel wall)
- “RULE OF 2s”
- 2% of normal population
- 2 ft from ileocecal valve
- Approx. 2 cm
- 50% have heterotopic mucosa; 2 types – gastric or pancreatic
- Complications: 1) inflammation (mimic appendicitis); 2) bleeding ulcer; 3) small bowel obstruction.



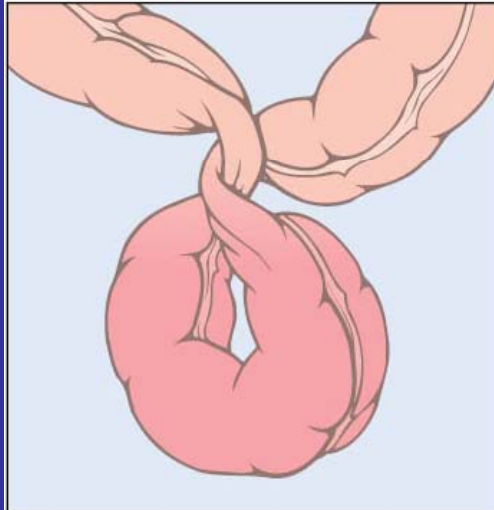
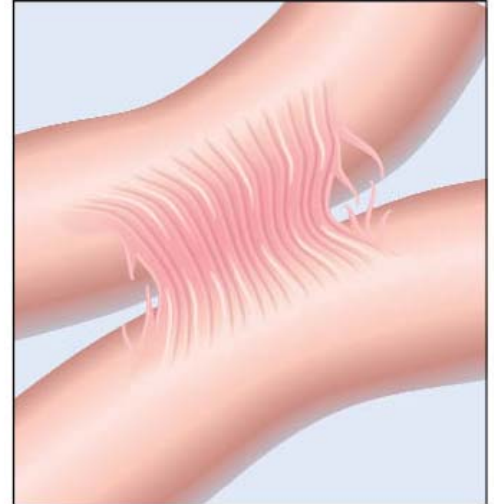


Intestinal Obstruction

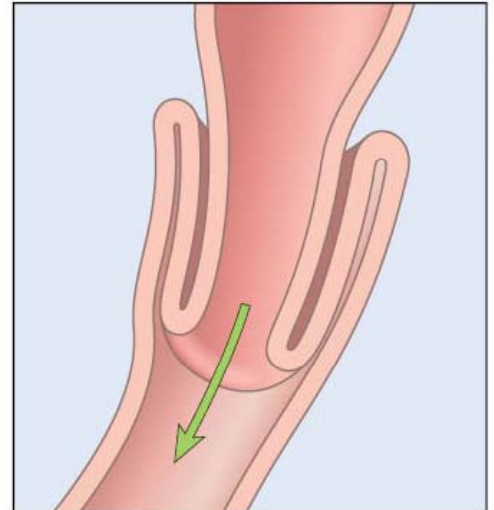
Herniation



Adhesions



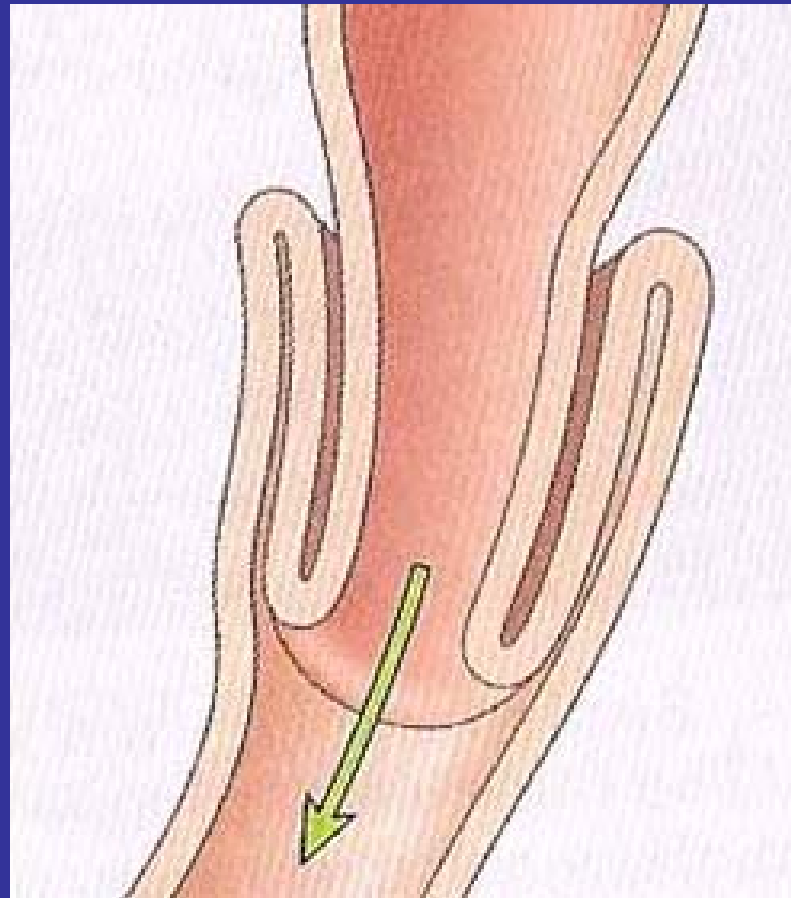
Volvulus



Intussusception

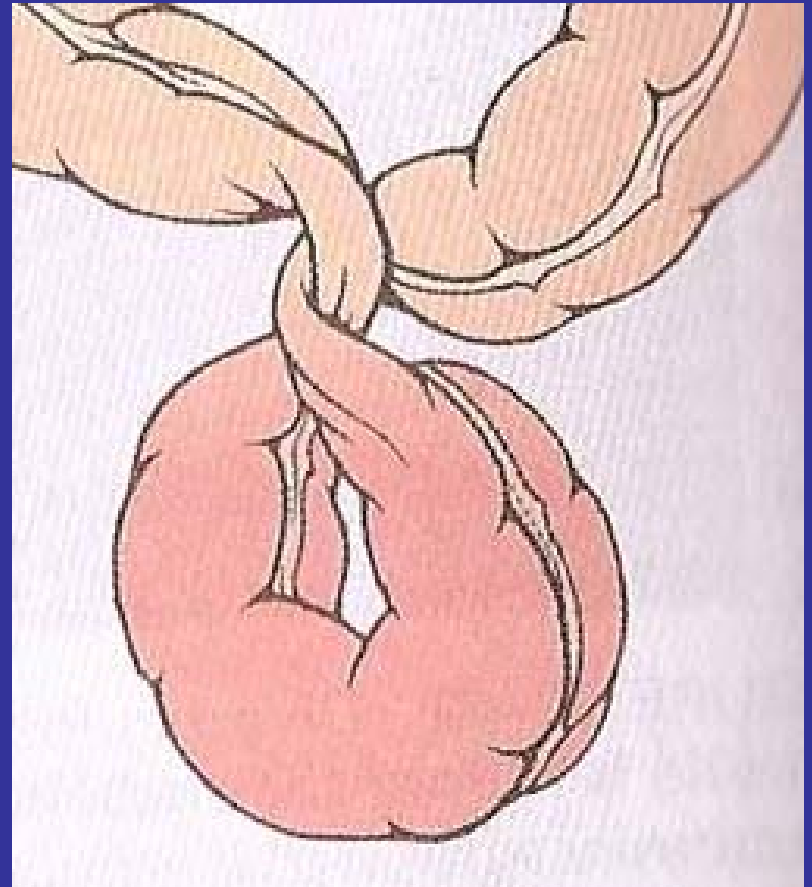
Intussusception

- Telescoping of one segment of bowel into another.
- Peristalsis propels the invaginated proximal segment farther into the distal segment.
- Spontaneous in children
- Secondary to intraluminal masses in adults
- Complications: obstruction, infarction



Volvulus

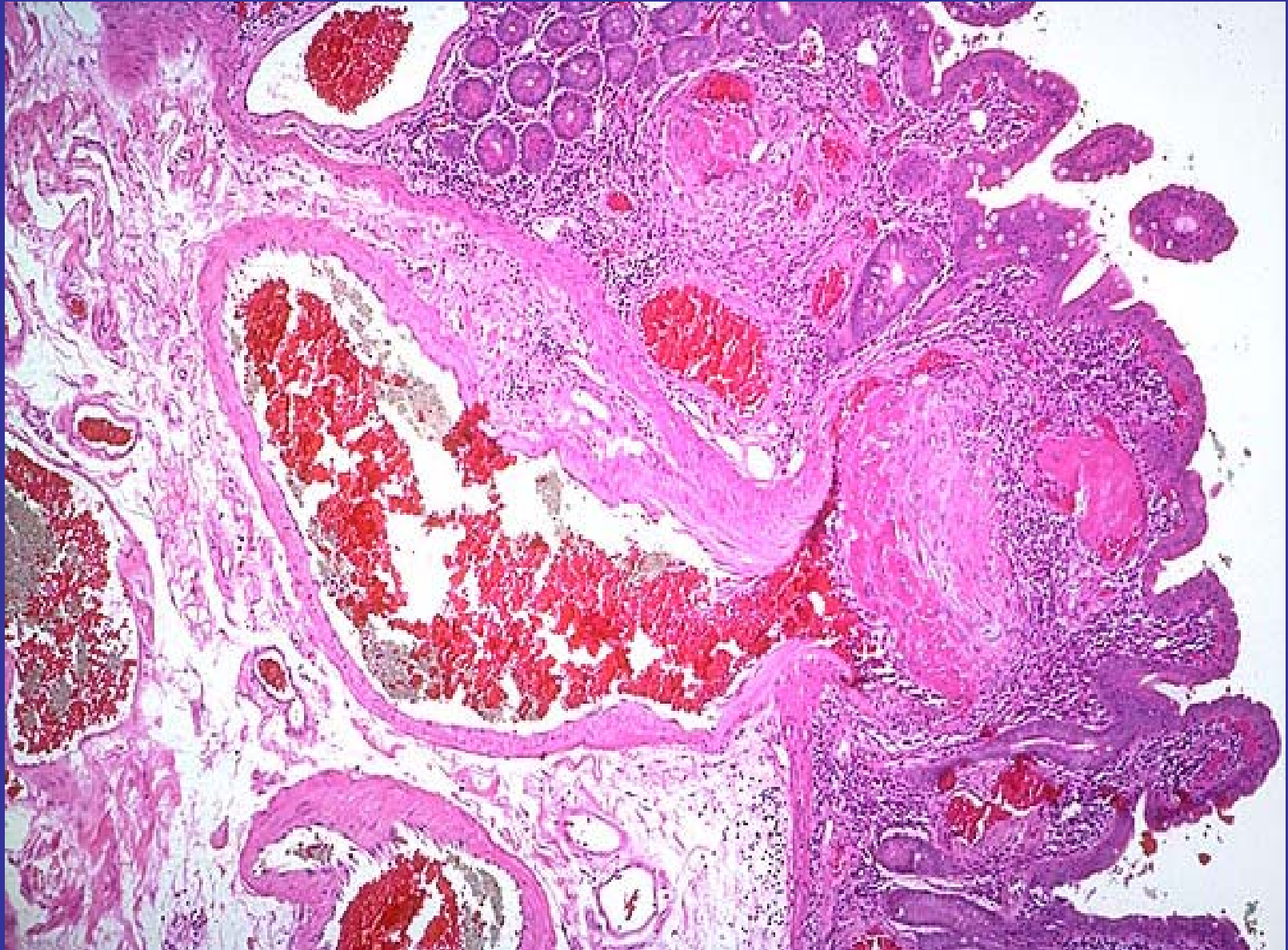
- Twisting of a loop of bowel around its mesenteric base.
- Sigmoid colon, cecum, small intestine, stomach, rarely transverse colon.
- Complications: obstruction, infarction.



Tumors of the Small Intestine

- Primary Tumors
 - Benign tumors (often found incidentally at surgery or autopsy)
 - Malignant tumors (intestinal obstruction or bleeding).
- Secondary Tumors
 - Metastatic carcinoma, melanoma, lymphoma.

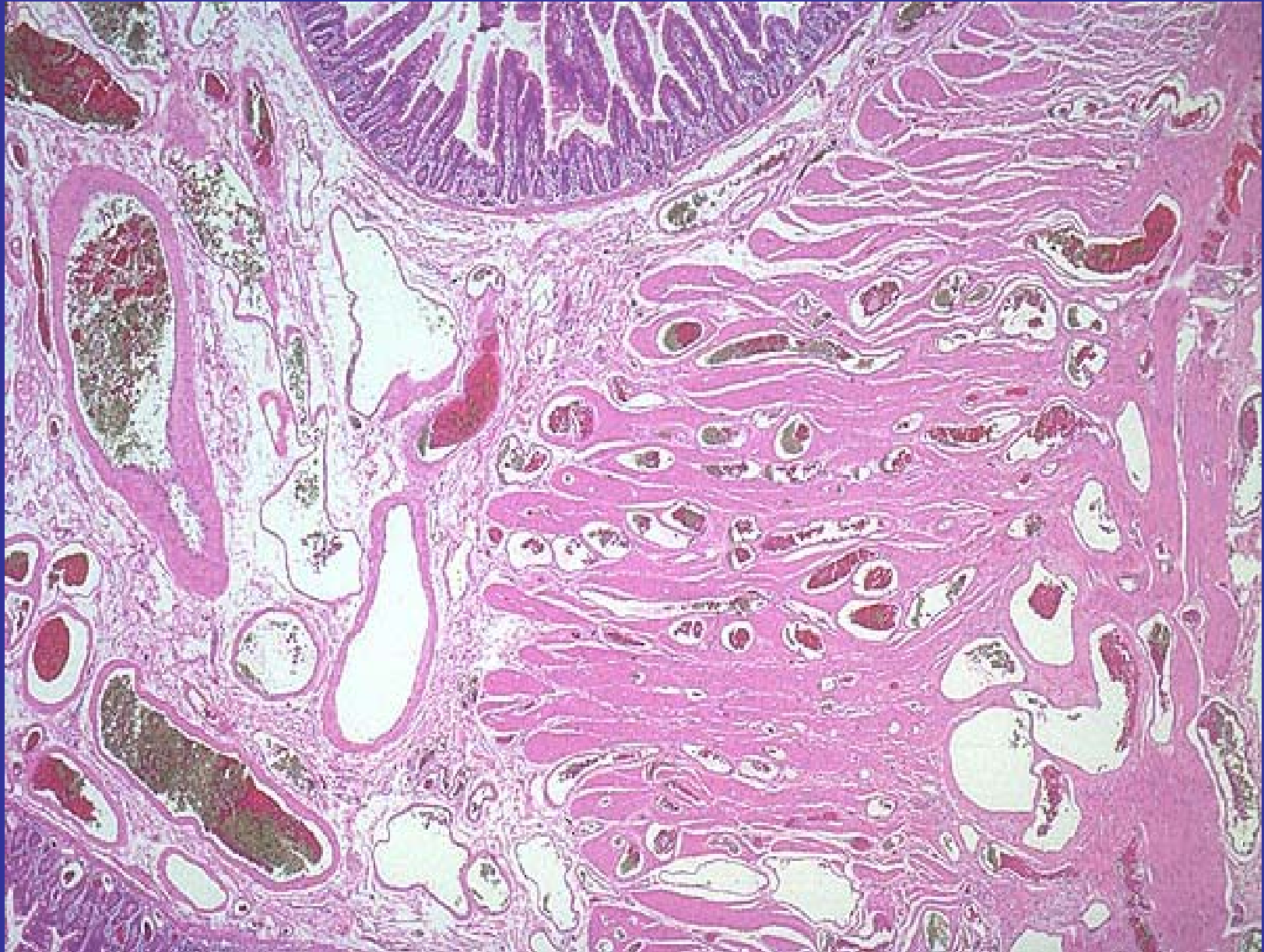
Vascular malformations



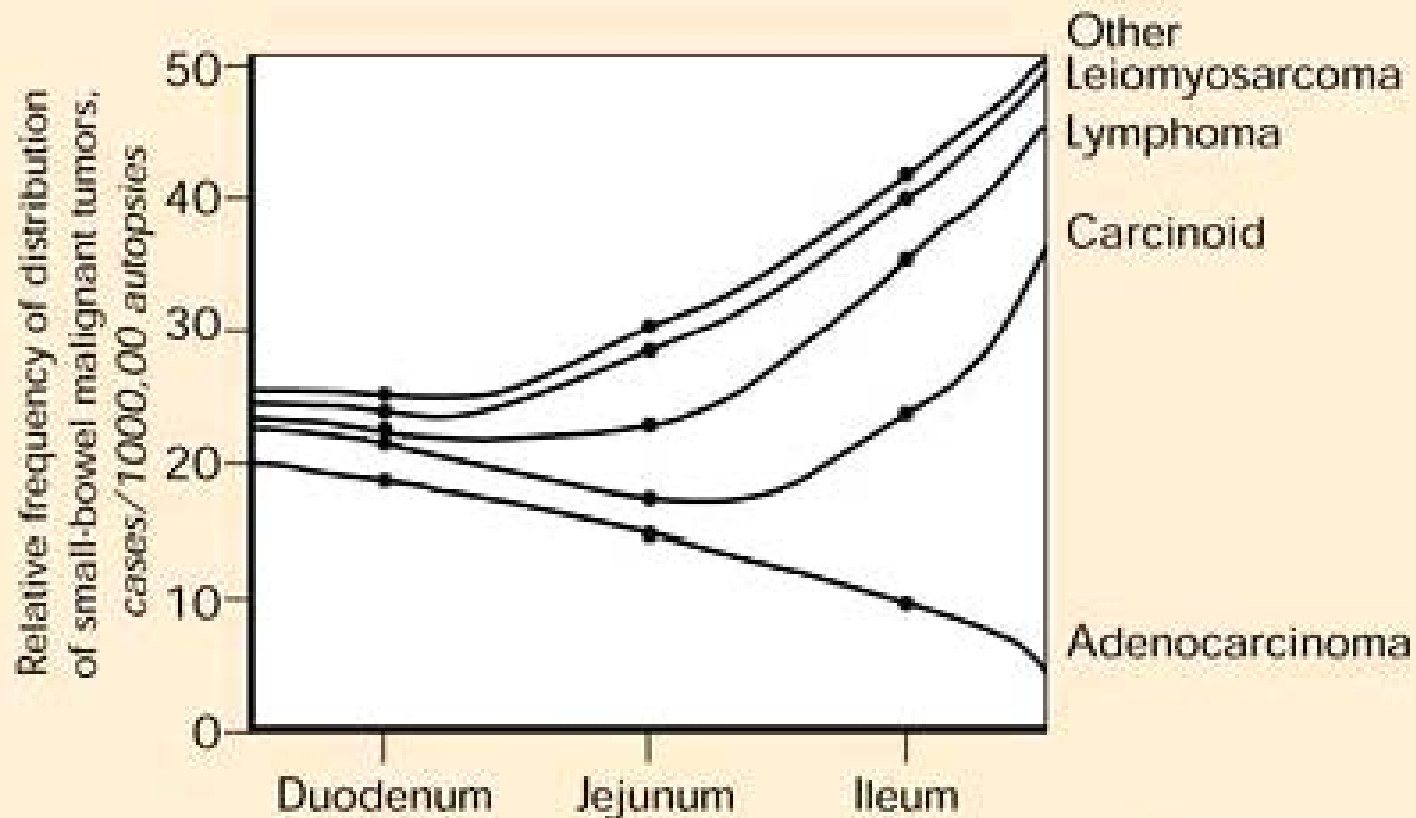
Hemangioma - submucosal



Vascular malformation – small intestine



Primary malignant neoplasms of Small Intestine



Small intestinal neoplasms often have similar signs and symptoms.

TABLE 39.9.3

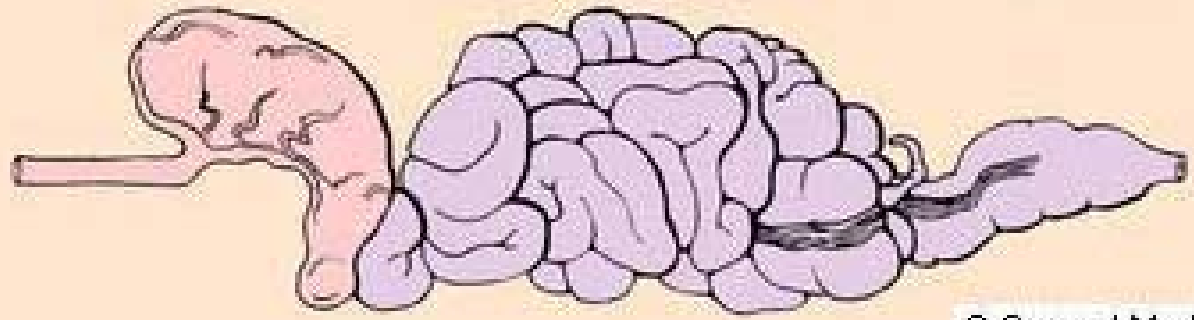
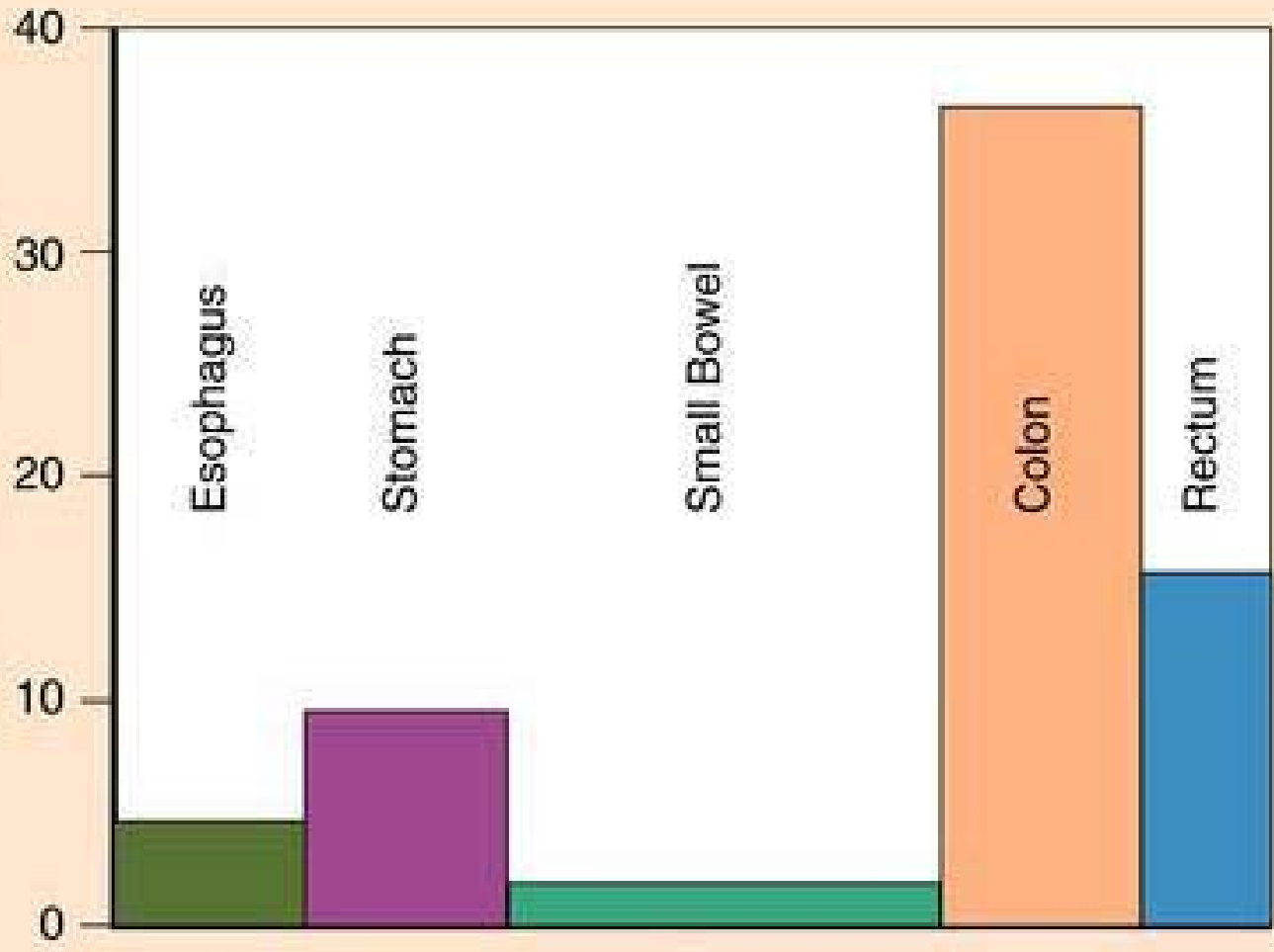
Presenting Signs and Symptoms of Cancer Arising in the Small Bowel in Several Large Series

	<i>Adenocarcinoma</i>	<i>Carcinoid</i>	<i>Sarcoma (GIST)</i>	<i>Lymphoma</i>
Abdominal pain	38–46	34	25	39–55
Obstruction	45–77	22–49	15	22
Perforation	2	0–2	0–2	15
Gastrointestinal bleed	12–26	0–2	30	4
Weight loss	21	25	0–5	52

GIST, gastrointestinal stromal tumor.
(From refs. 9–12, 15, 24, with permission.)

Copyright © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

U.S. annual incidence of malignant gastrointestinal tumors, new cases/100,000/year



Carcinomas of the Small Intestine: why are they so rare?

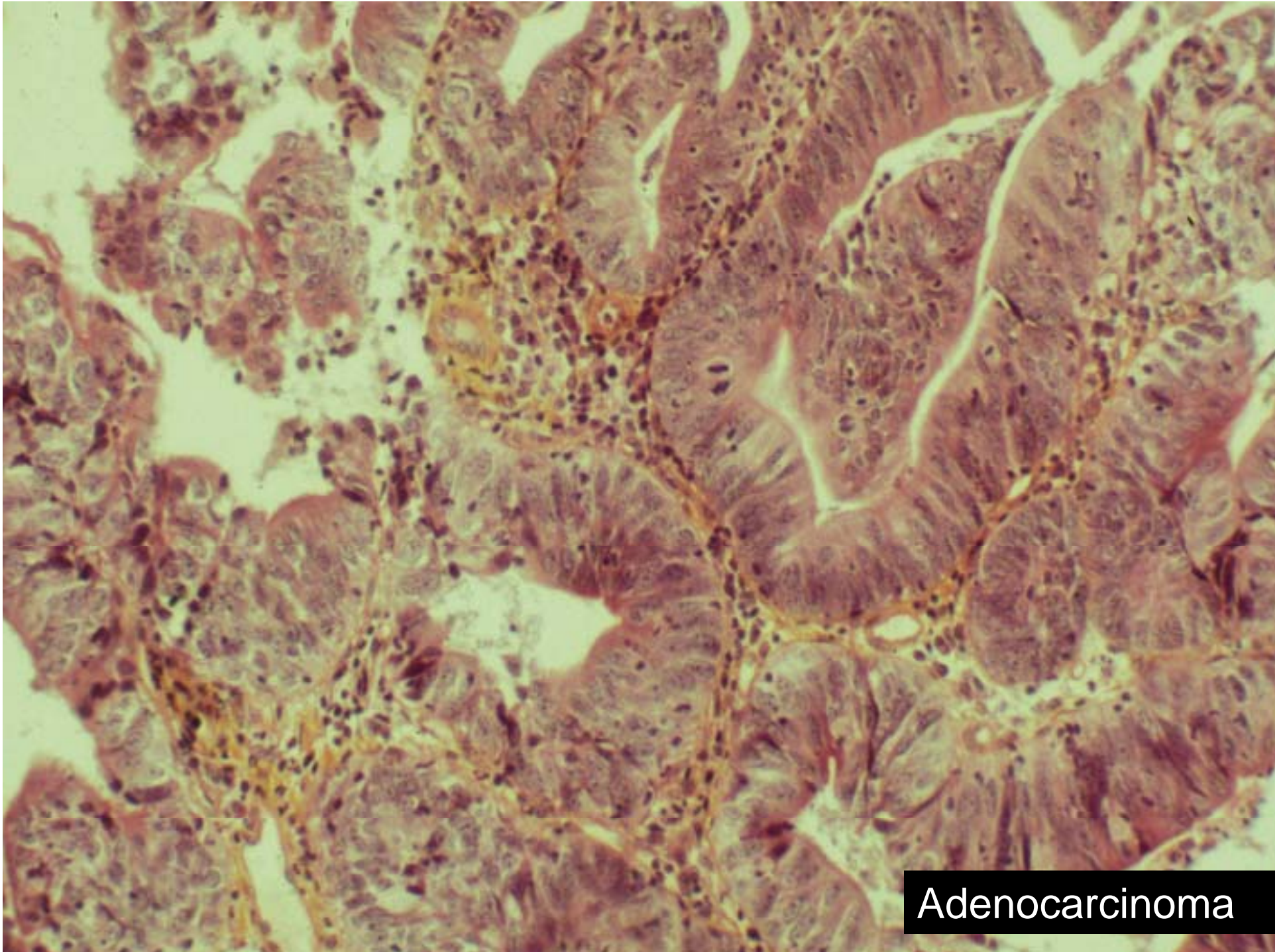
- Rapid transit of small bowel contents
- Smaller bacterial load
- Increased lymphoid tissue

Carcinomas of the Small Intestine

- Most common location: duodenum, periampullary, least common: ileum
- Growth patterns: annular constricting or polypoid masses
- Symptoms: Obstruction and/or bleeding
- Predisposing conditions: Celiac disease and Crohn's disease; FAP; HNPCC



Adenocarcinoma



Adenocarcinoma

Small Intestinal tumors – Predisposing conditions.

TABLE 39.9.2

Genetic and Environmental Conditions that Predispose to Cancer of the Small Intestine

<i>Condition</i>	<i>Histology</i>
Familial adenomatosis polyposis	Adenocarcinoma
Hereditary nonpolyposis colon cancer	Adenocarcinoma
Crohn's disease	Adenocarcinoma
Peutz-Jeghers	Adenocarcinoma, hamartomas
Gardner's syndrome	Adenocarcinoma, desmoid
Celiac disease	Adenocarcinoma, lymphoma
Neurofibromatosis	Paraganglioma
AIDS	Lymphoma
History of other primary cancer	Adenocarcinoma, carcinoid

Small Intestinal Carcinomas have similar molecular profile as CRC

TABLE 39.9.5

Genetic Abnormalities Found in Adenocarcinomas Arising in the Small Intestine

<i>Authors (Reference)</i>	<i>No. of Tumors Examined</i>	<i>Mutations in p53</i>	<i>Mutations in K-ras</i>	<i>Mutations in APC</i>	<i>Mutations in RER</i>
Blaker et al. (75)	17	—	—	3/17	2/17
Hamilton	15	6/15	6/15	5/15	2/15
Arai et al. (77)	15	4/15	—	3/15	NA
Wheeler et al. (76)	21	5/21	—	0/21	1/21
Planck (78)	89	—	—	—	16/89
Nishyama	35	14/35	2/35	—	—
Achille	12	8/12	5/12	6/10	3/12
Zhang	54	NA	NA	8/26	2/25
EXPECTED COLON CANCER		40%–80%	40%–80%	40%–60%	15%–20%

N/A, not available.

Carcinoid Tumors of the GI Tract

- GI tract is the most common site of carcinoids (67%)
- Small intestine is the most common site of GI carcinoids, followed by rectum and appendix
- Prognosis is SITE and SIZE dependent

Small intestinal carcinoids

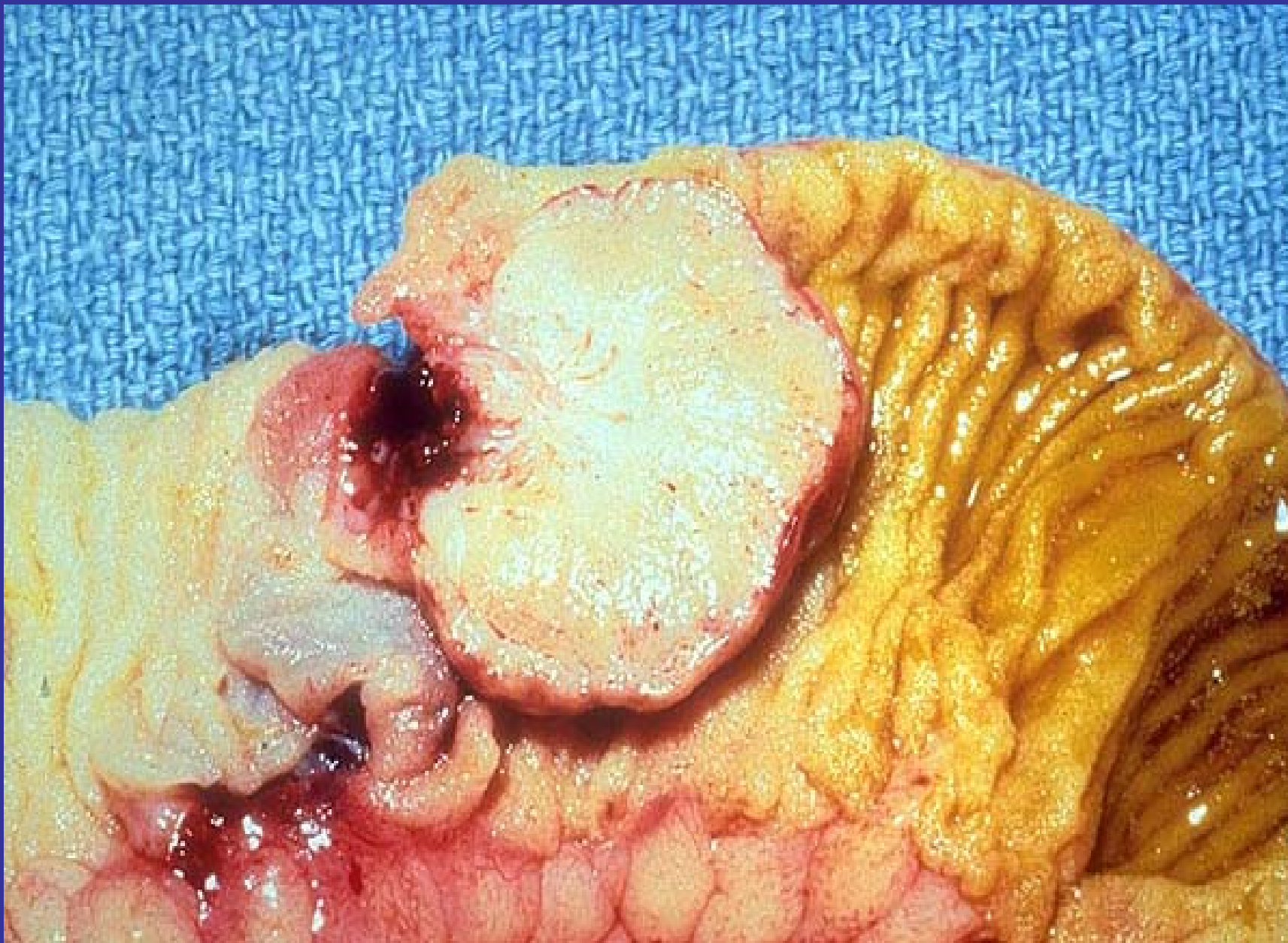
TABLE 39.9.7

Risk of Metastases from Carcinoid Tumors Arising in the Small Intestine

<i>Size of Primary Tumor</i>	<i>Risk of Metastases (%)</i>
<6 mm	15
6–10 mm	31
>10 mm	73

(From ref. 109, with permission.)

Terminal ileum- 2.5 cm tumor

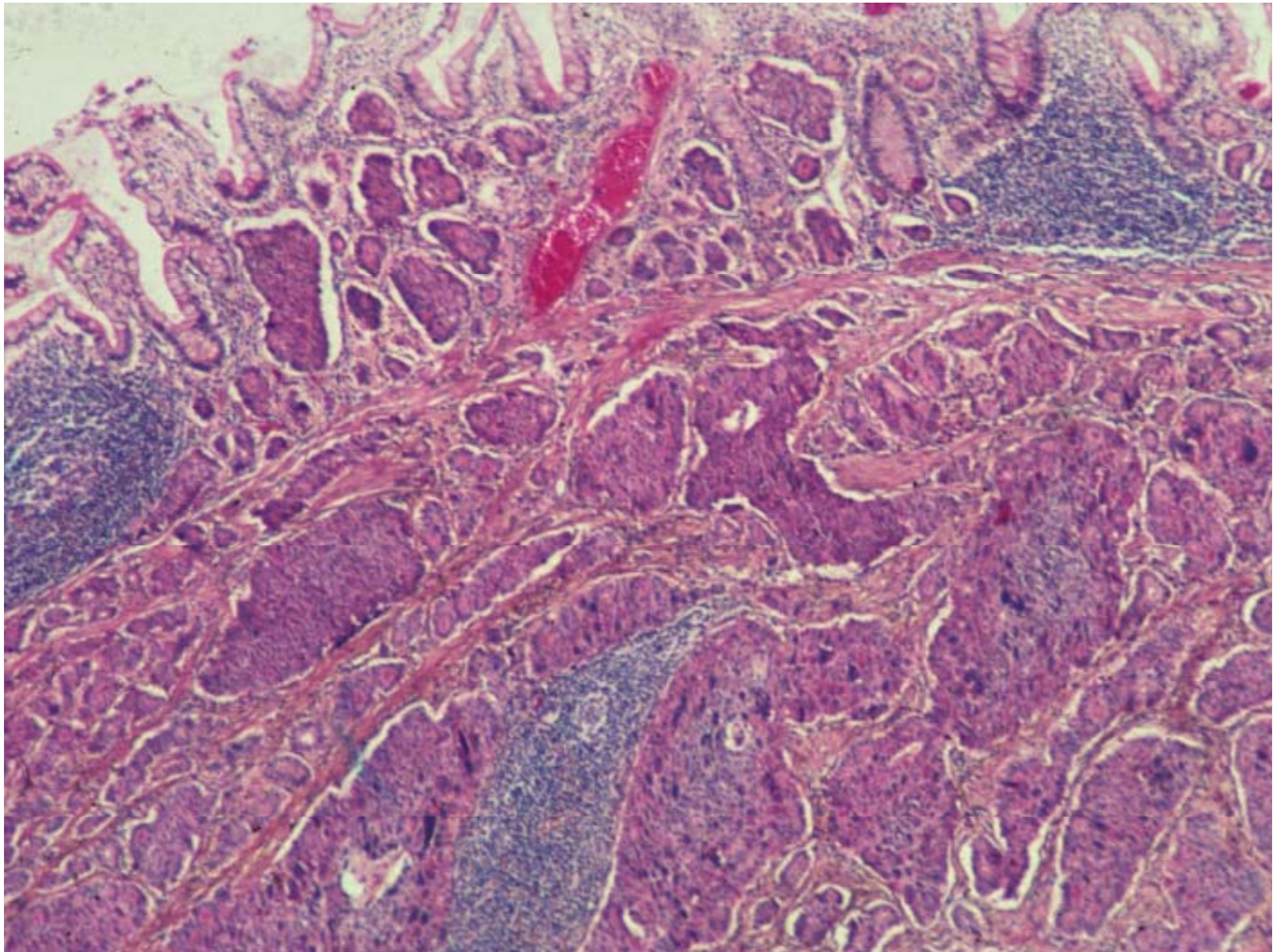


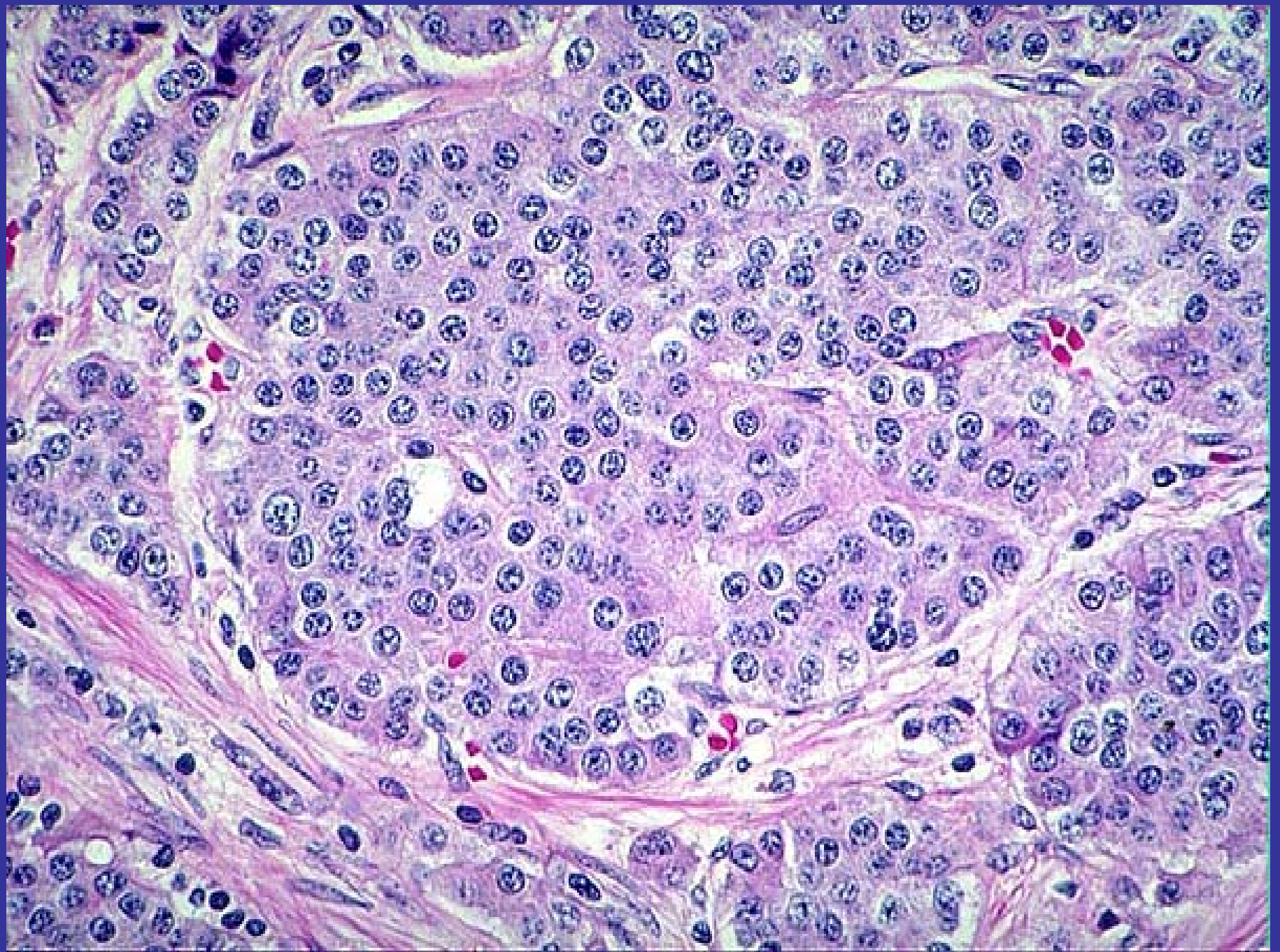
Carcinoid tumor- Ileum



Ileal carcinoid tumor- “kinking of bowel wall”







Carcinoid Tumor: Prognosis

- 68% 5 yr survival after resection (as compared to 25-35% for adenocarcinoma).
- 38% 5 yr survival after incomplete resection
- 21% 5 yr survival with liver mets

Carcinoid Syndrome (small bowel carcinoid tumors)

- Only in patients with liver mets.
- Cutaneous flushing, diarrhea, bronchospasm, right heart failure.
- Serotonin, bradykinin, substance P, prostaglandins.
- Elevated 5 HIAA (5 hydroxy-indol-acetic acid – metabolic product of serotonin) in urine.

GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal Stromal Tumors (GISTs) are a distinct group of mesenchymal tumors of the GI tract.

Most common mesenchymal neoplasms in the GI tract.

Mesenchymal tumors of the GI tract

GIST (GI stromal tumors)

Fibromatosis
Desmoid

Schwannoma

Leiomyoma

Neurofibroma

Hemangioma

Lipoma

Granular
Cell tumor

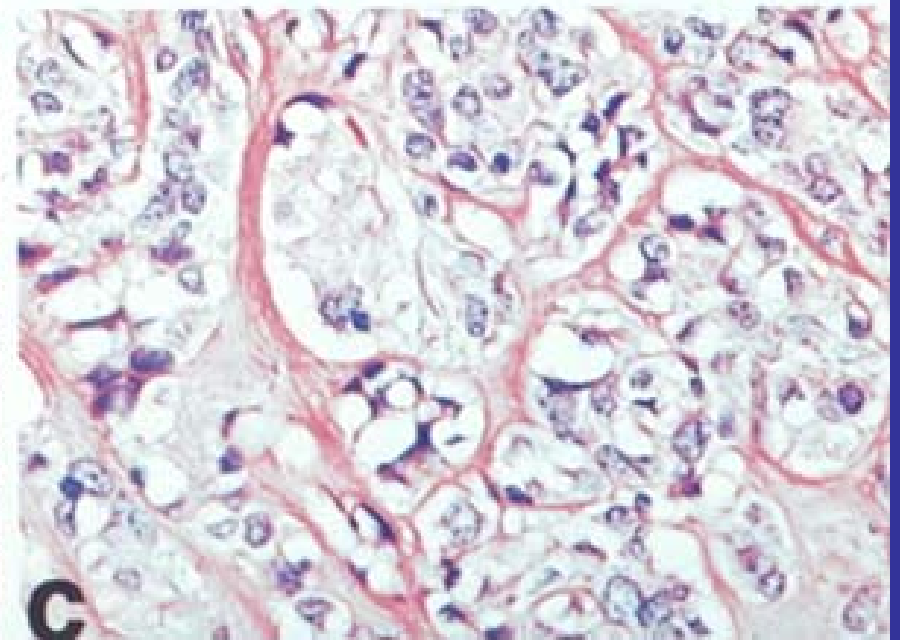
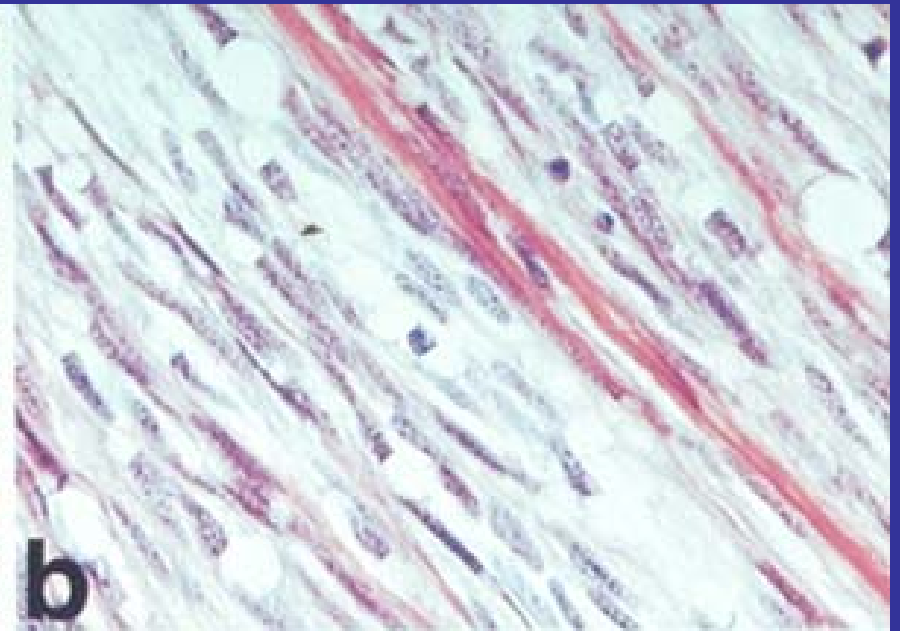
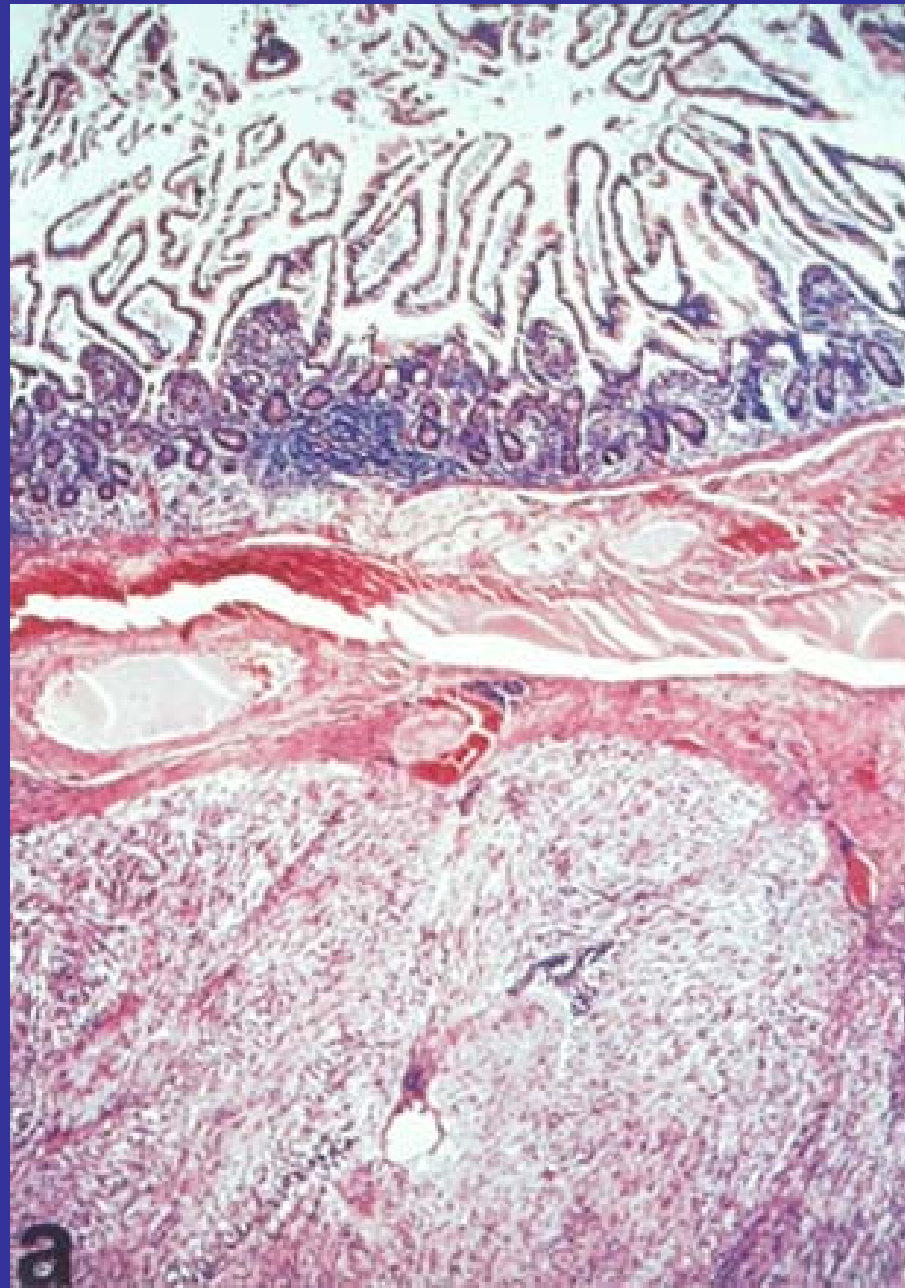
Leiomyosarcoma

MPNST

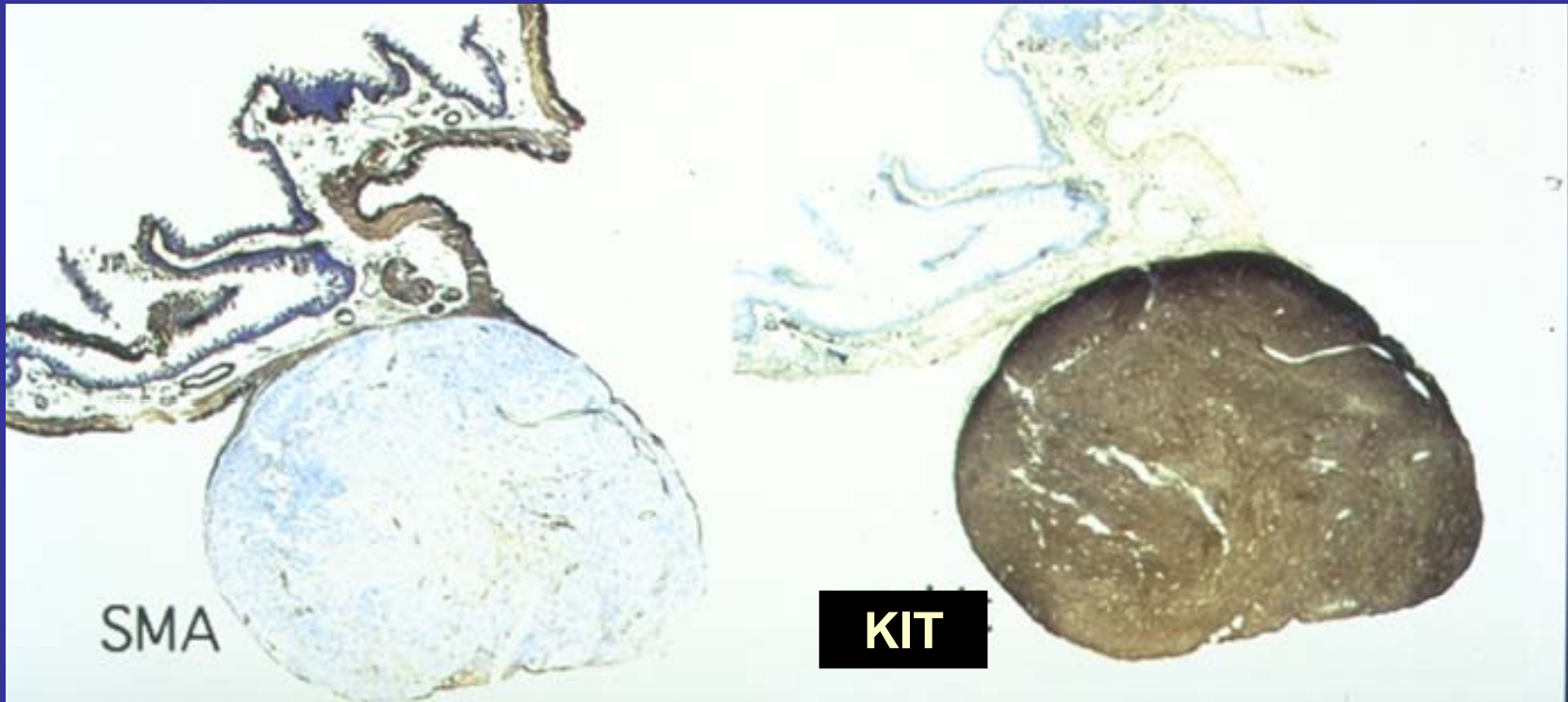
Metastatic neoplasms

Benign

Malignant



GISTs have a distinctive immunophenotype.



KIT

The *KIT* proto-oncogene encodes a **type III receptor tyrosine kinase (KIT)**, the **ligand** of which is **stem cell factor (SCF)**.

SCF-KIT interaction is essential for development of :

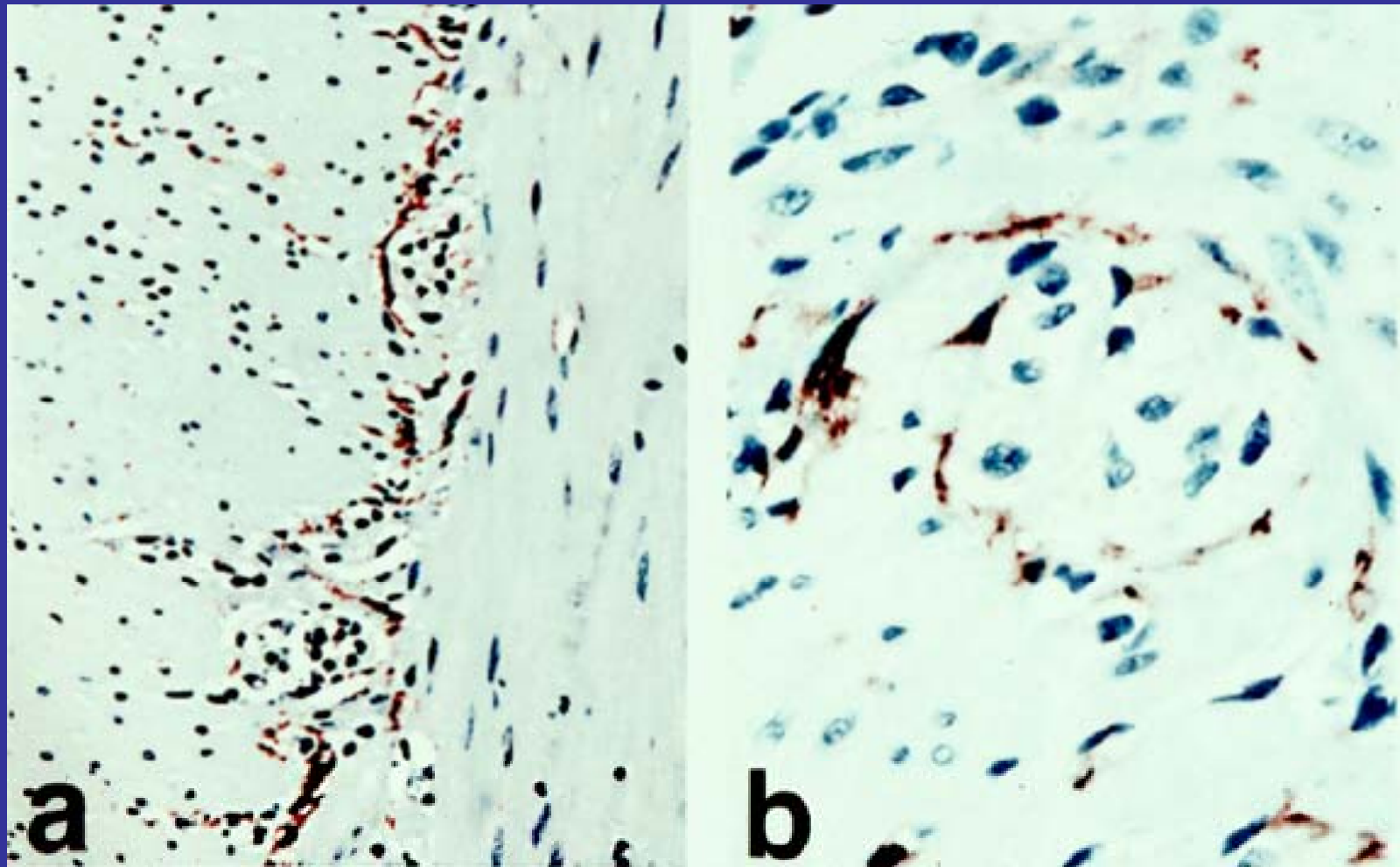
Melanocytes

Germ cells

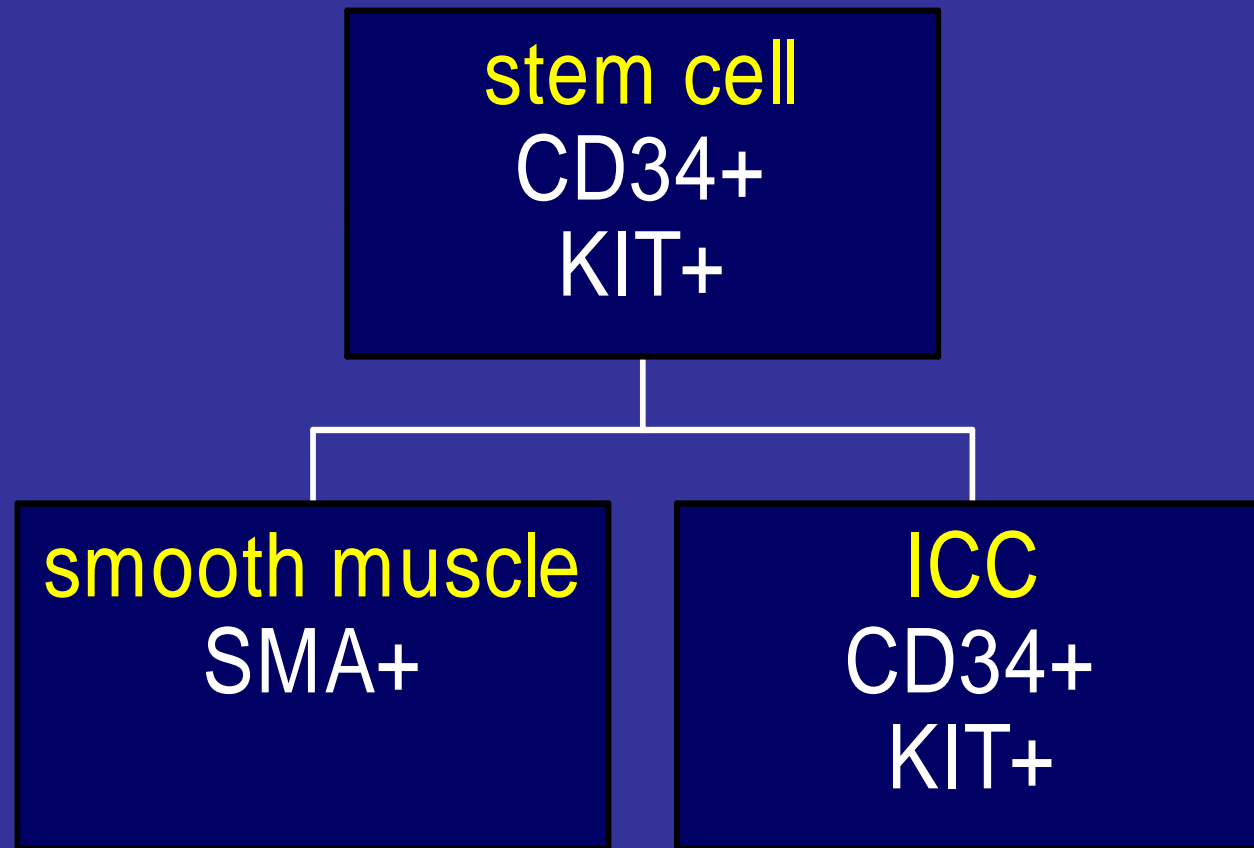
Mast cells

Interstitial cells of Cajal (ICC) / gut pacemaker cells.

**INTERSTITIAL CELLS OF CAJAL (ICC)
Pacemakers cells of the gut KIT+**



Proposed GIST histogenesis



KIT mutations

Loss of function
(*Ws/Ws* mice and rats)

Defects in:

- melanogenesis
- hematopoiesis
- gametogenesis
- intestinal motility

(Huizinga et al, 1995)

Gain of function

(Human tumors and animal models)

Malignant transformation in:

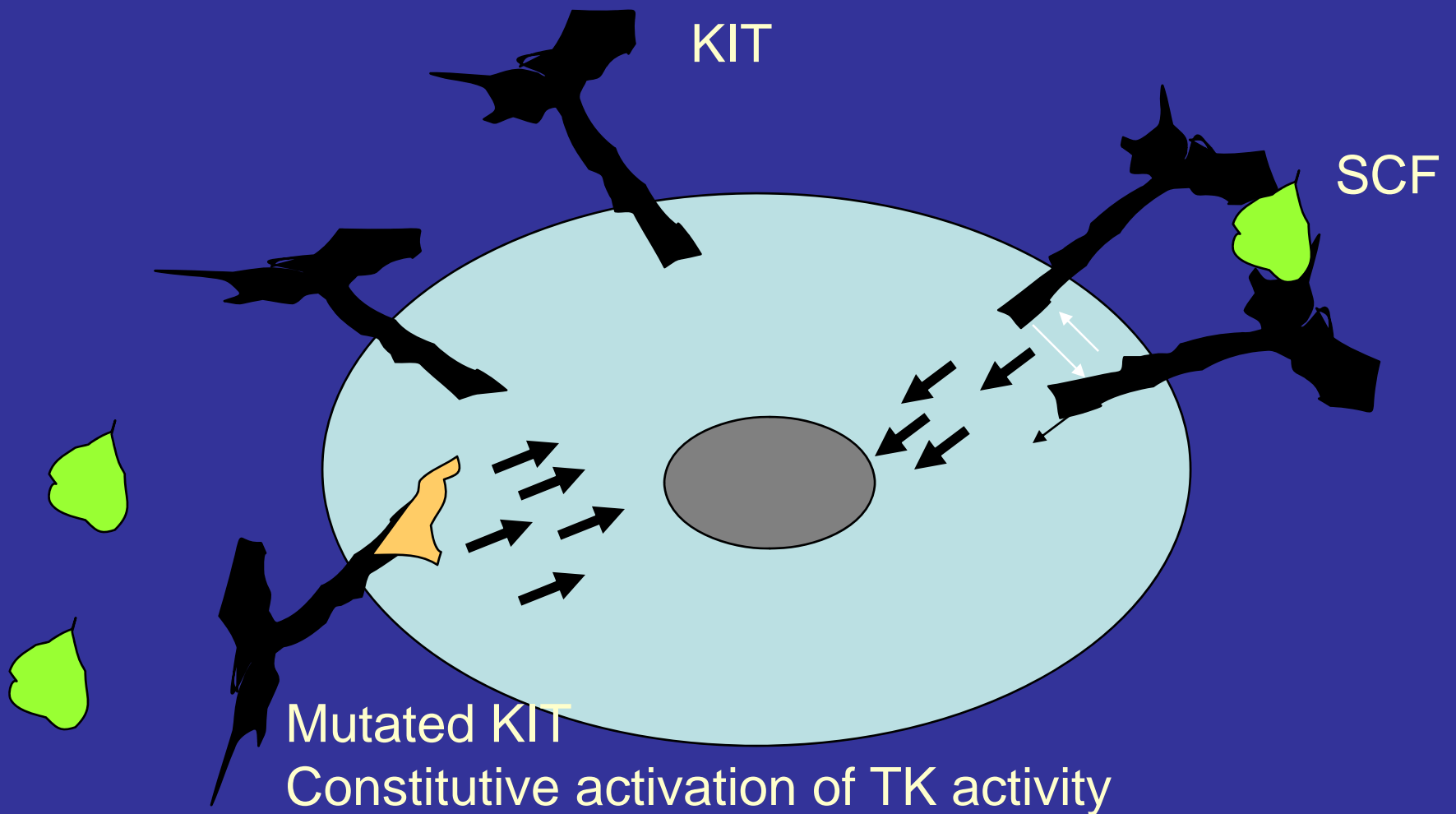
Melanoma

Mast cell neoplasms

Gastrointestinal stromal tumors

(Nagata et al, 1992, Longley et al, 1997).

KIT receptors bind to Stem Cell Factor (SCF) leading to cross phosphorylation leading to downstream signal transduction pathways.

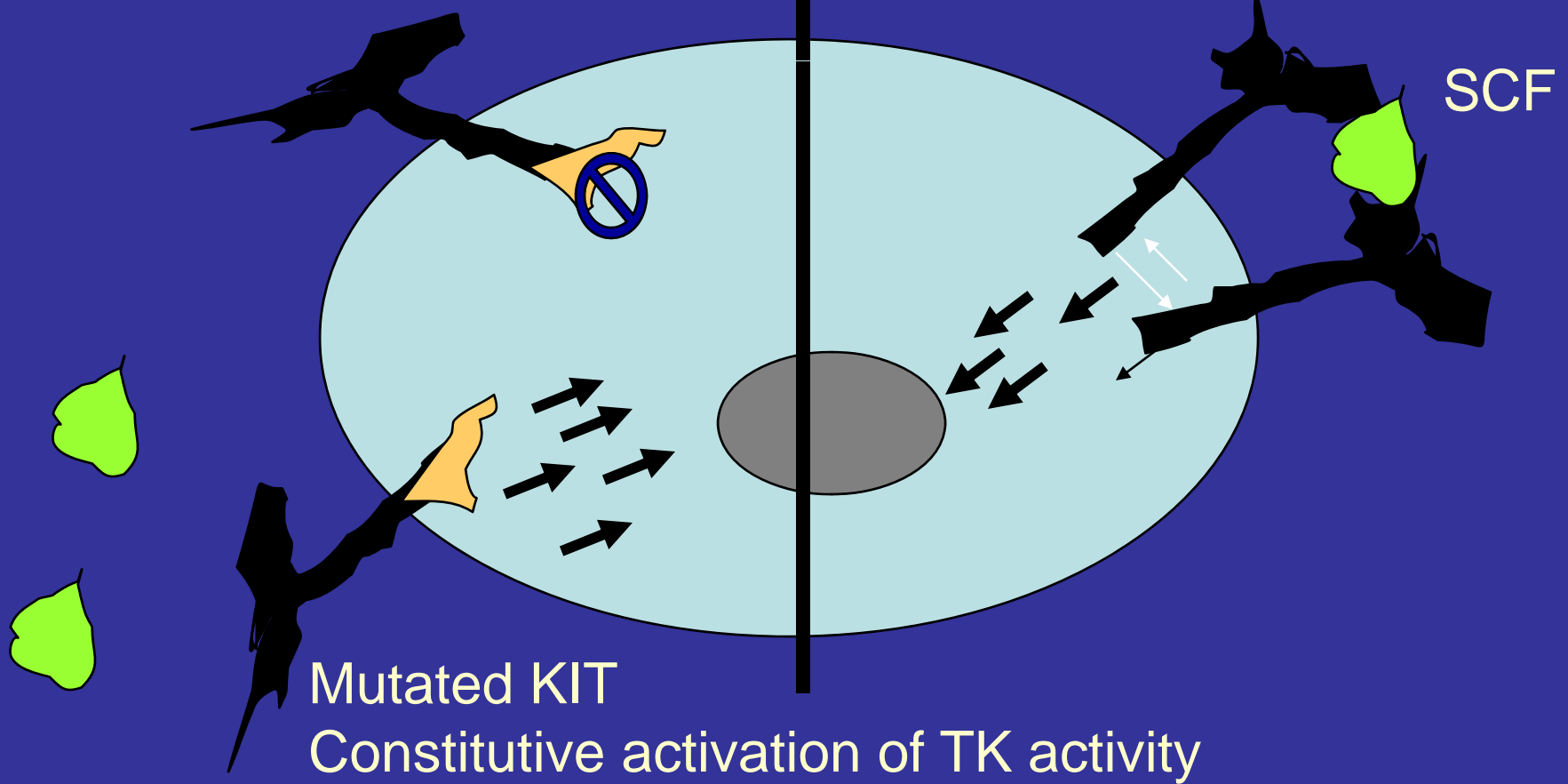


tyrosine kinase inhibitors

KIT mutant

KIT wild type

SCF



GIST Treatment

- (STI571 – Tyrosine Kinase Inhibitor)
- Gleevec, Imatinib, (Novartis, Basel Switzerland)
- Approved for treatment of CML, in which BCR-ABL tyrosine kinase is activated.
- STI 571 blocks the ATP binding site of kinase domain.
- Clinical trials for CML in 1999 showed dramatic response rates 100%. Drug was well tolerated.

1999 –in vitro studies with GIST cell lines (D.Tuveson, J. Fletcher) showed that STI571 blocked TK activity.

STI571-In vivo trial in GIST patient

First patient with metastatic GIST treated with STI571/Gleevec:
50 yr old female with multiple recurrent, metastatic GIST.

Multiple liver mets (>28)

Tumor : KIT Immunoreactive

Documented activating mutation in exon 11 of *KIT*

Progressive disease despite all available prior therapies:

Gastrectomy, (Mesna, Adriamycin, Ifosfamide, Dacarbazine),
resection of mets, IFN-alpha.

· Joensuu H, et al. *NEJM*, April 5, 2001, p1052-1056

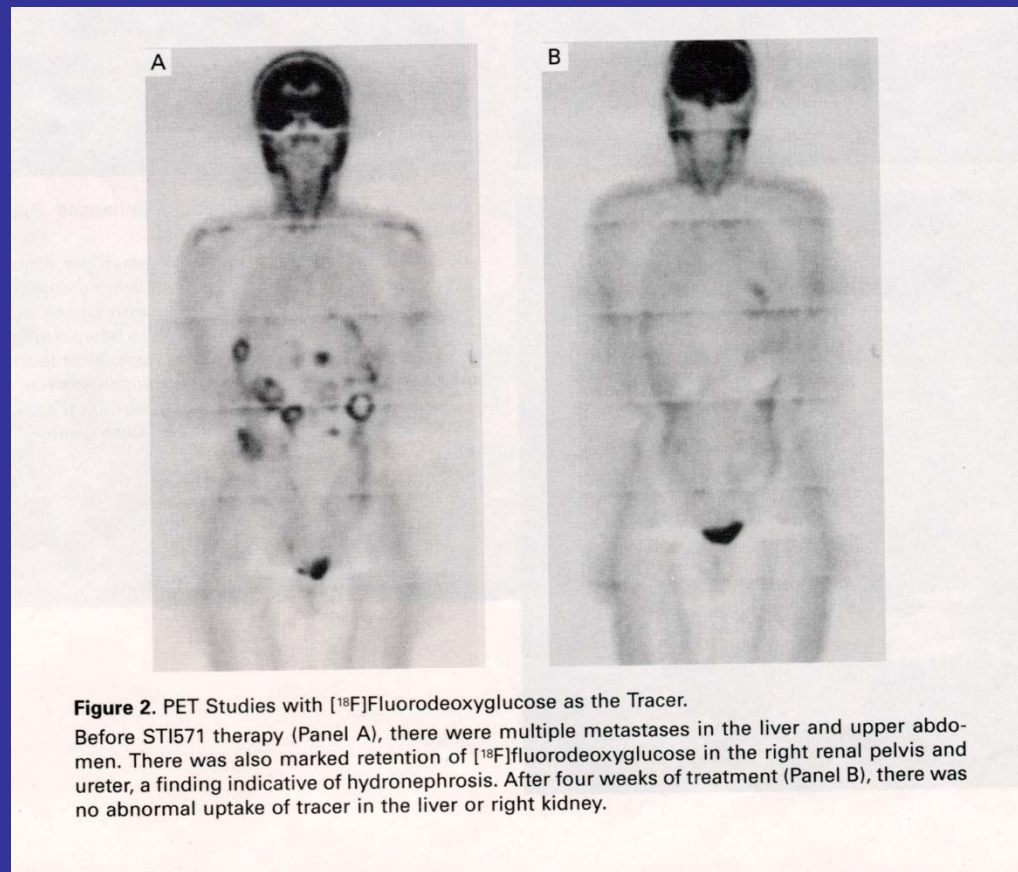
STI571-In vivo trial in GIST patient

Tumor mets became metabolically inactive on PET scan.

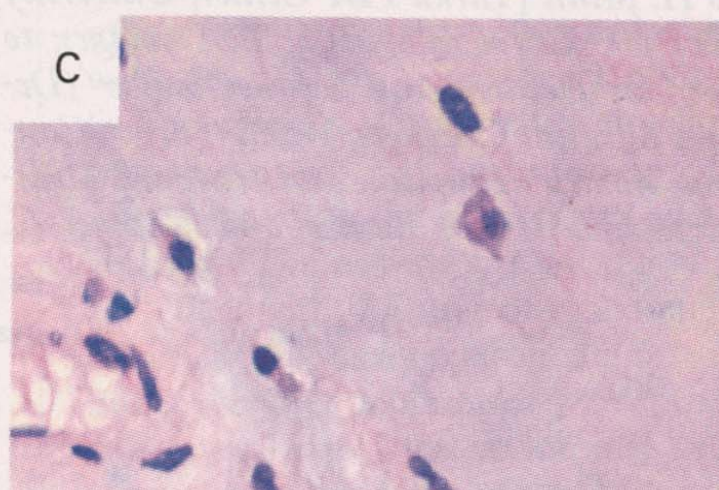
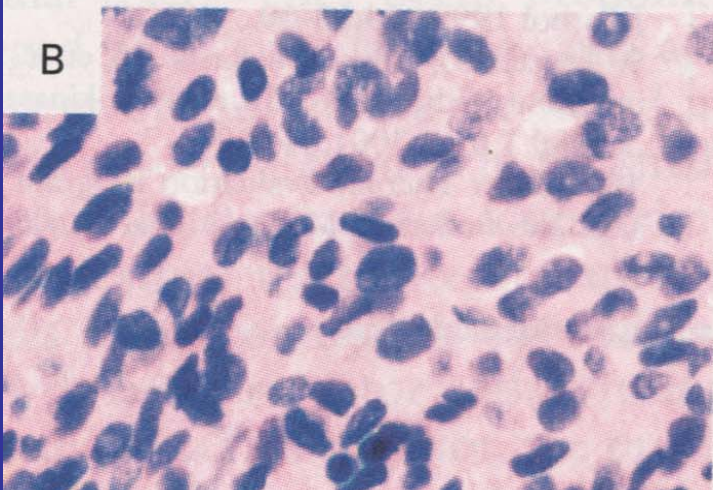
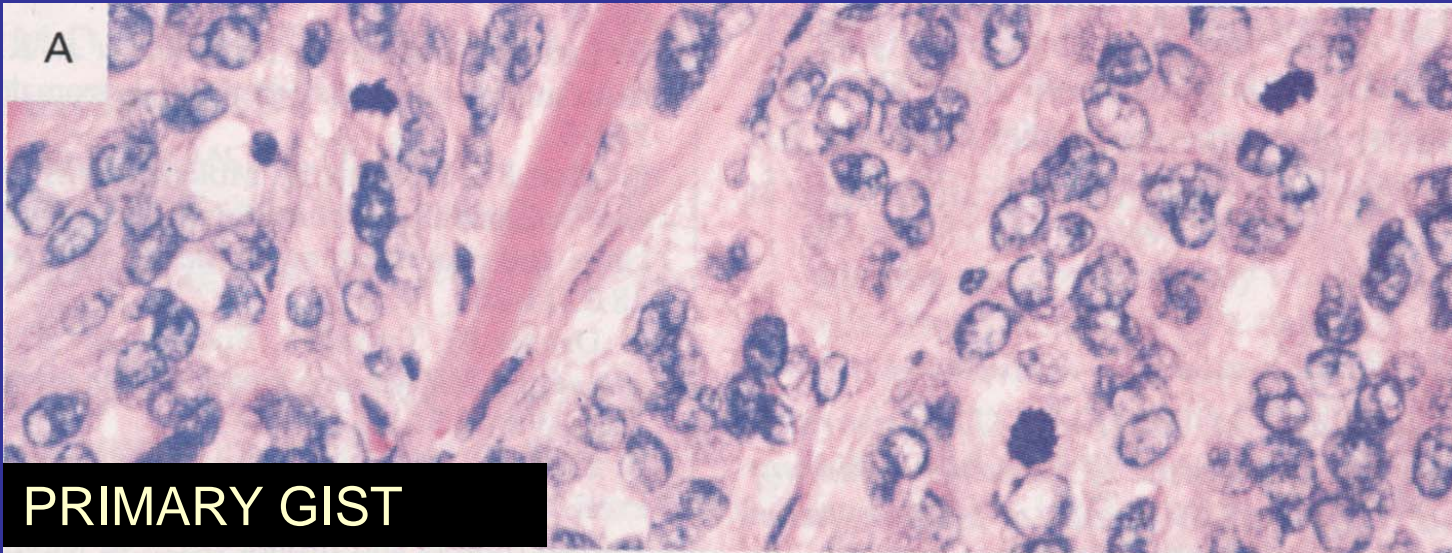
Showed marked improvement in symptoms; metastases decreased in size and tumor showed myxoid degeneration.

Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

First GIST patient treated with STI571/Gleevec FDG-PET scans before and after 4 week treatment



Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

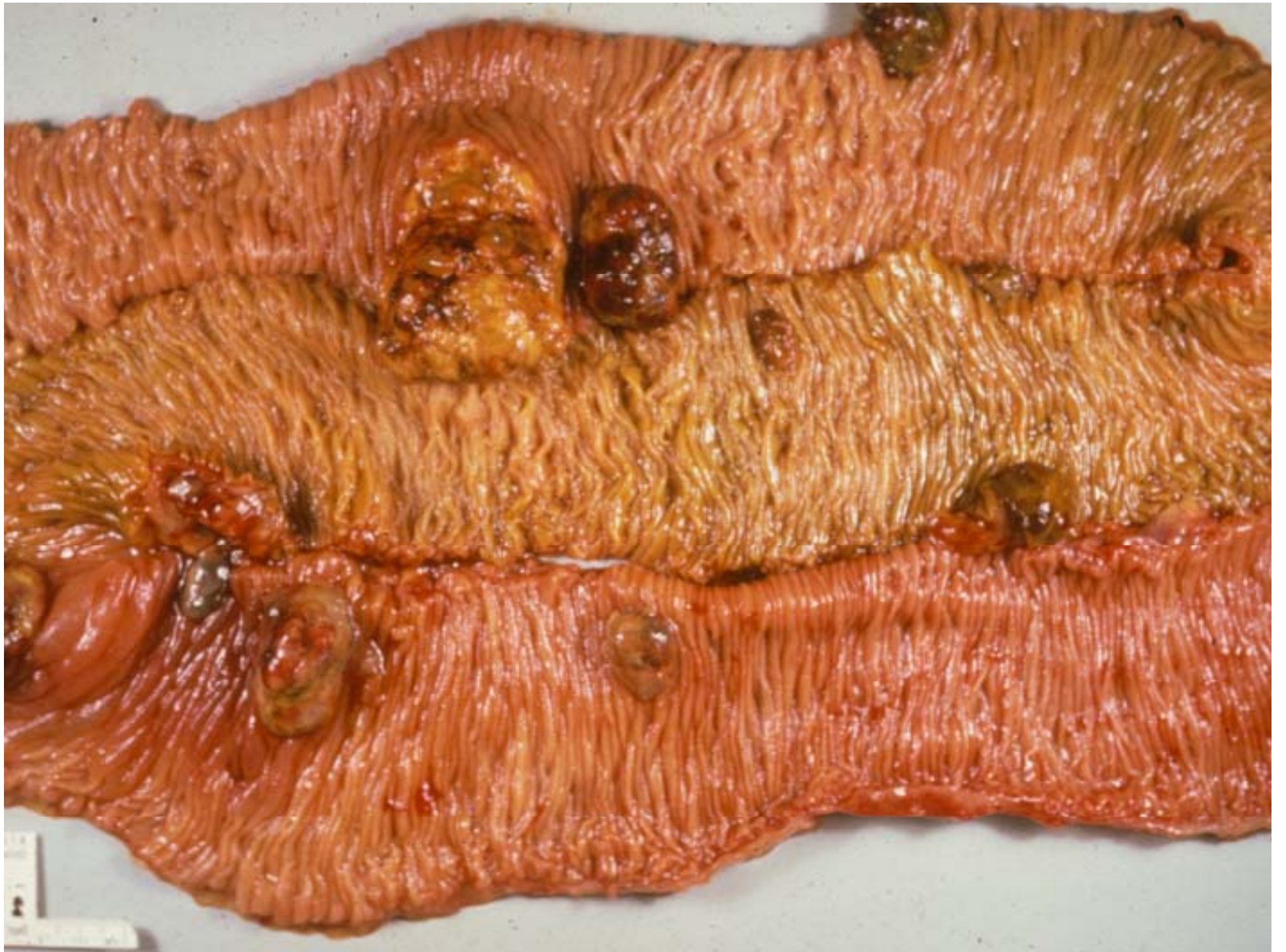


LIVER MET B) before STI571 C)after 4 weeks of STI571

Joensuu H, et al. NEJM, April 5, 2001, p1052-1056.

Aquired STI571/Gleevec resistance in GISTs

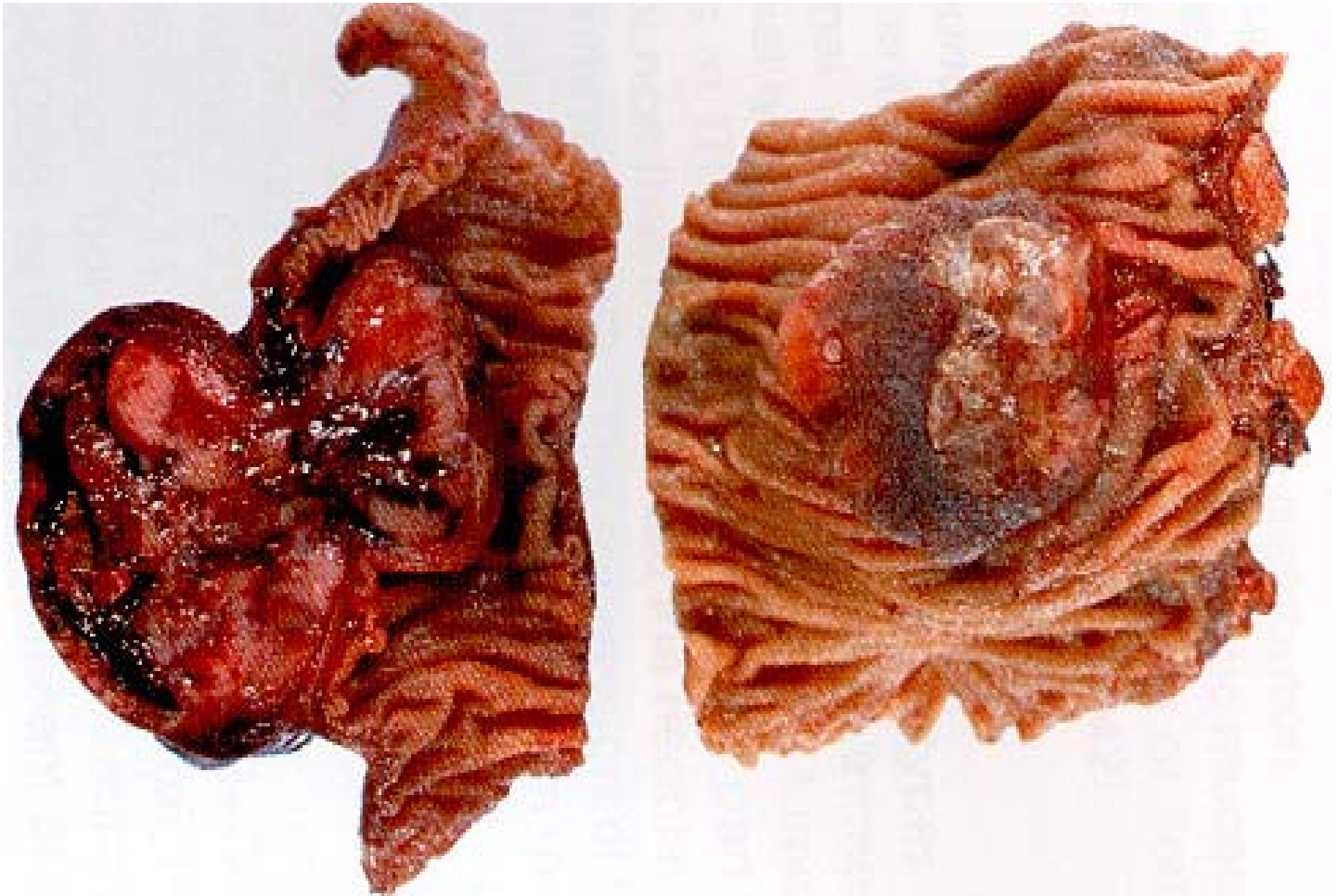
- Majority of patients who initially benefit from tyrosine kinase inhibitors eventually become resistant.
- Median time to progression on imatinib of 2yrs.
- Mechanism of resistance – additional KIT mutation often affecting binding of drug.



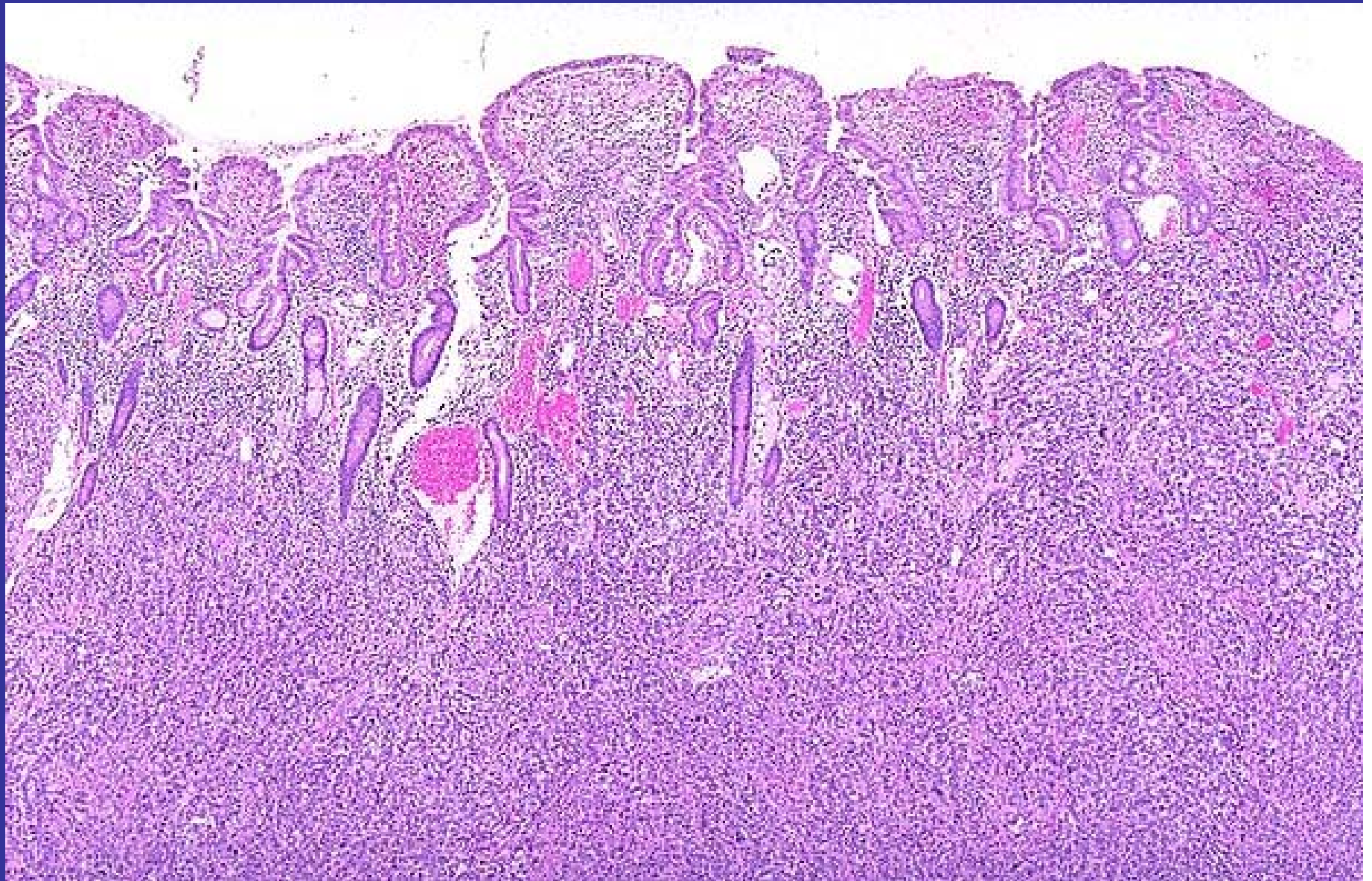


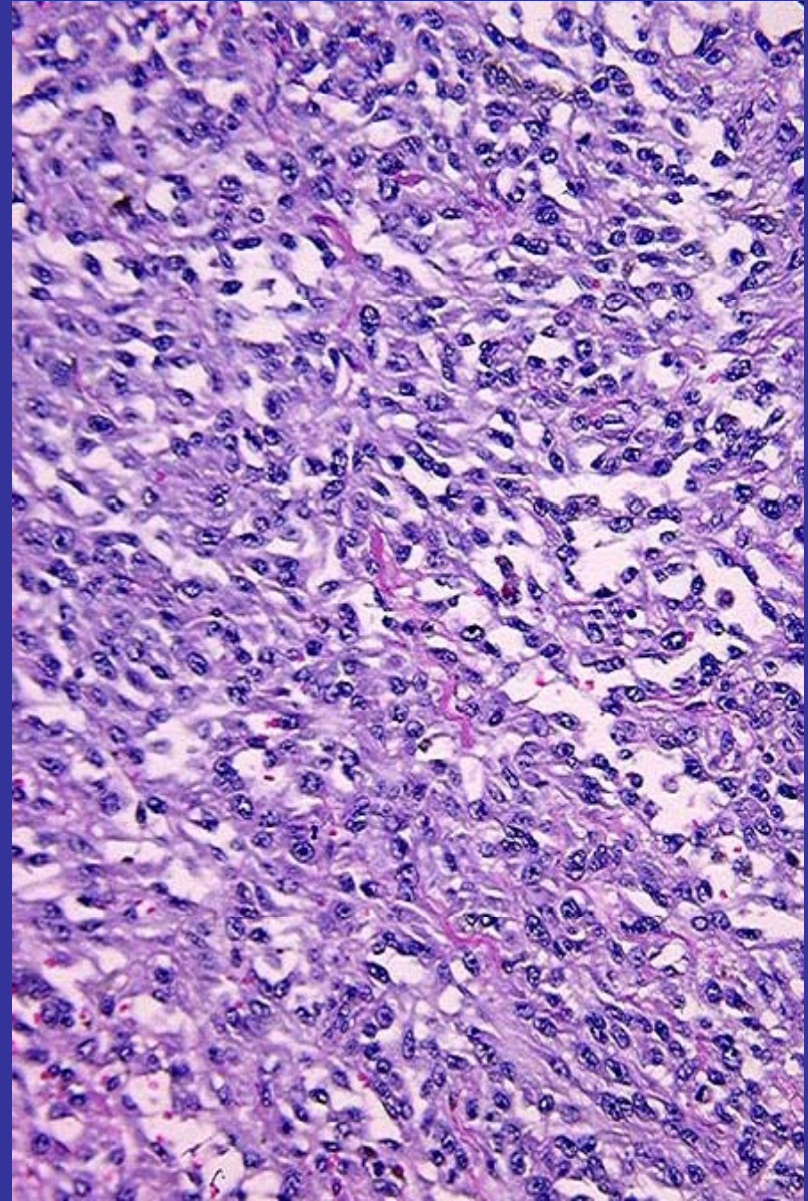
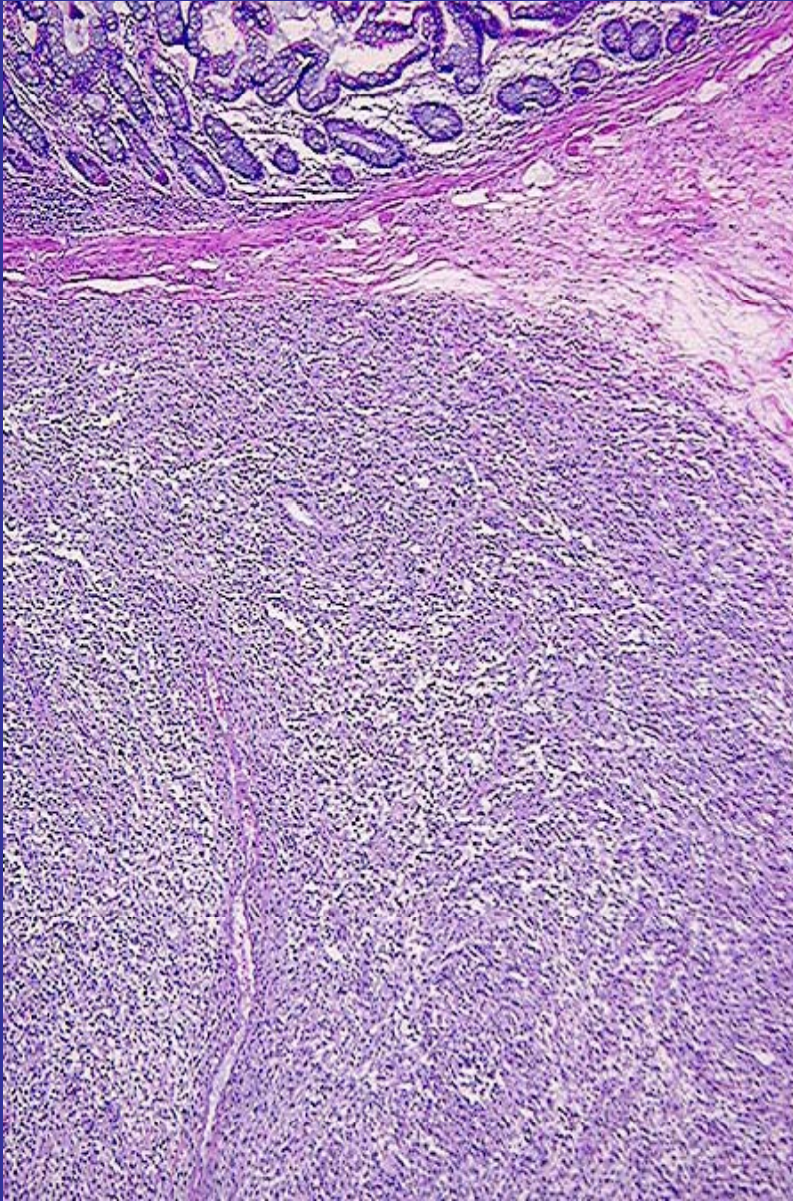
Metastatic Neoplasms

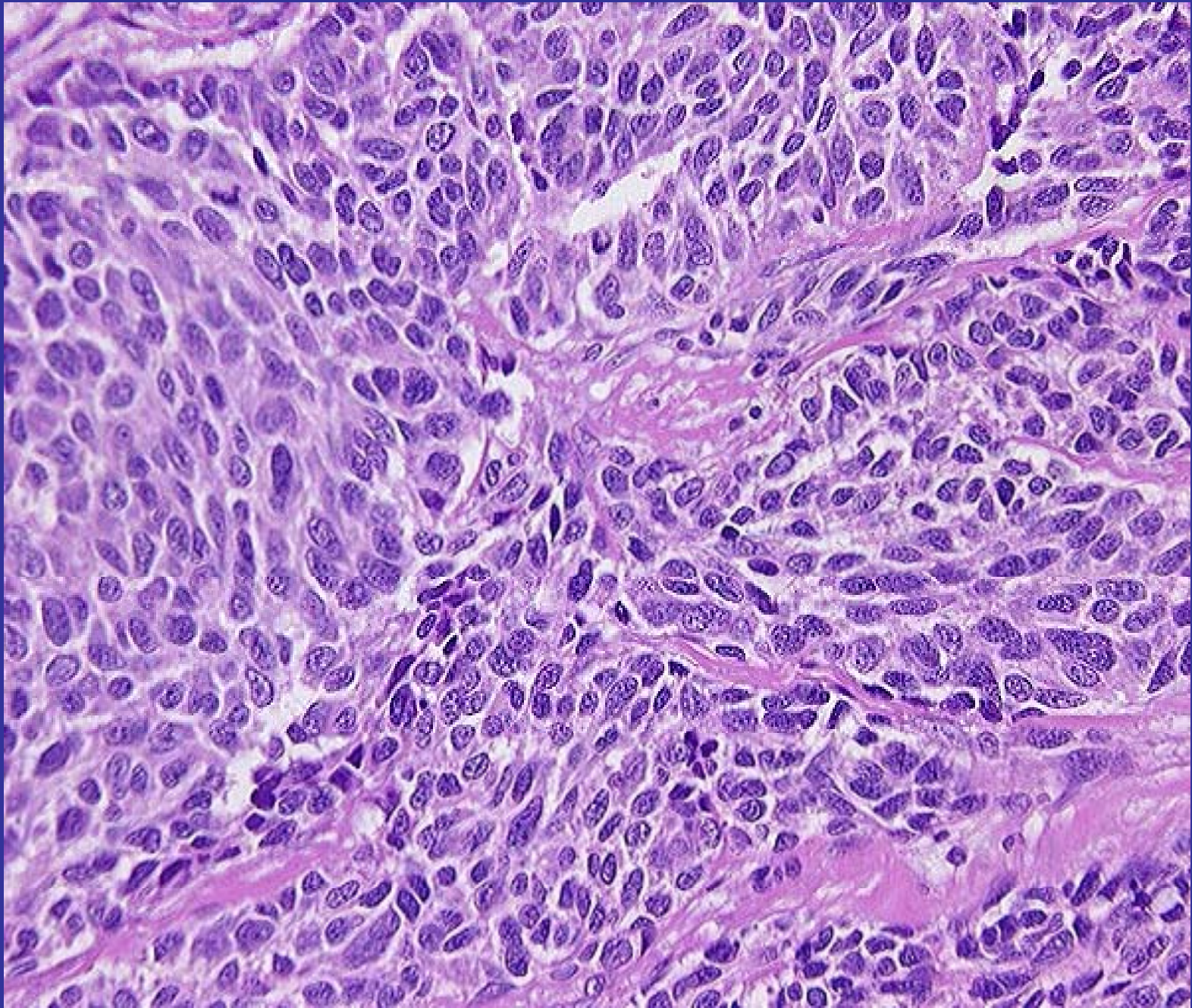
- Always consider metastatic neoplasms in the small intestine – very commonly occur.
- Think metastatic lesion –if there is no associated in-situ lesion or if multiple nodules or serosal based nodules present.

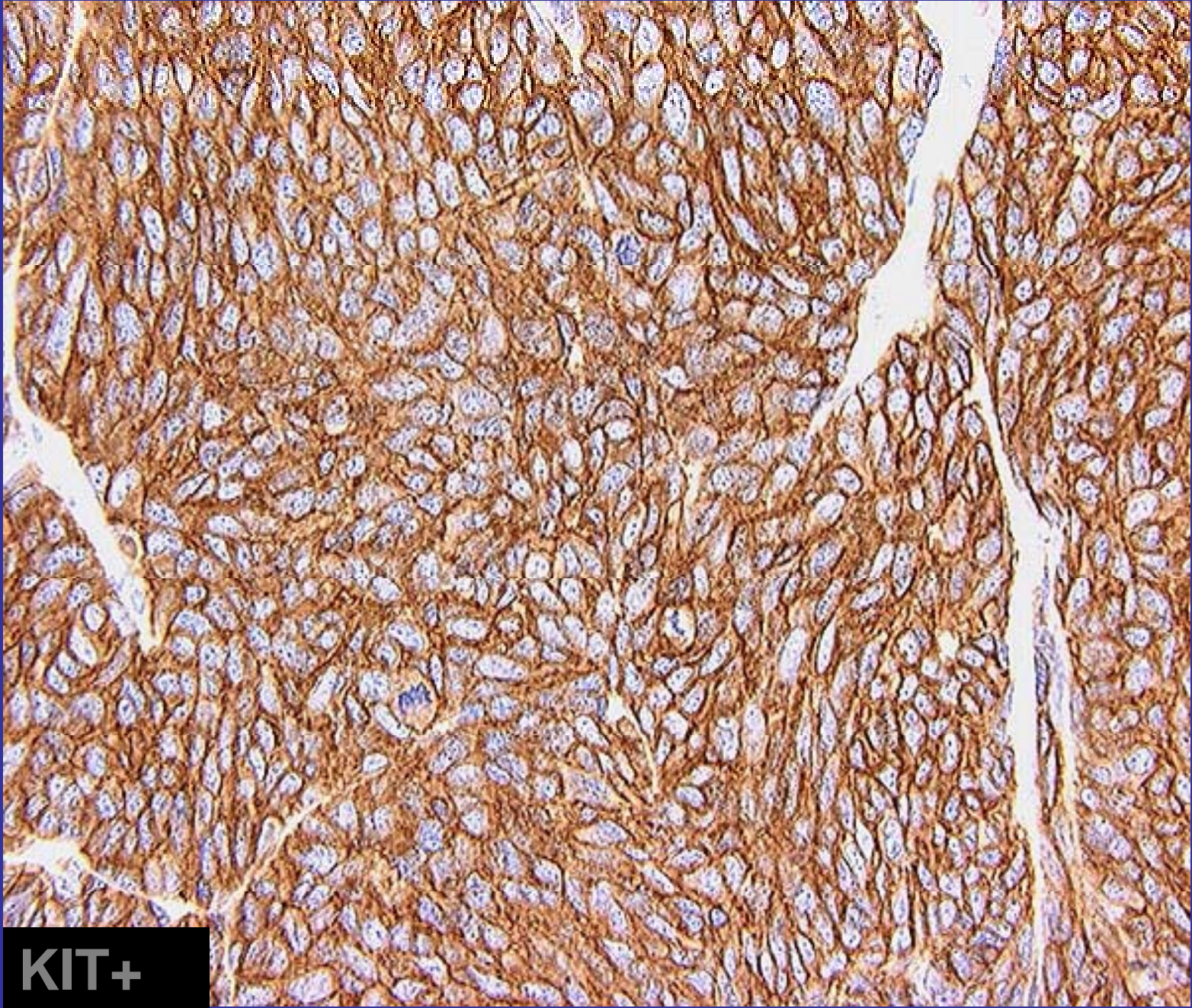


66 y.o. male with 8 cm mass within the wall of the jejunum

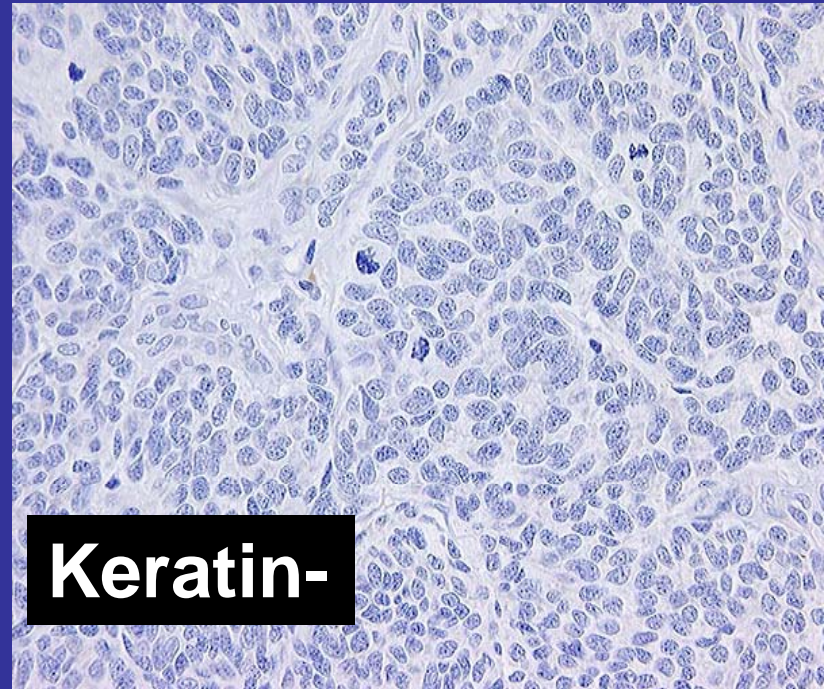
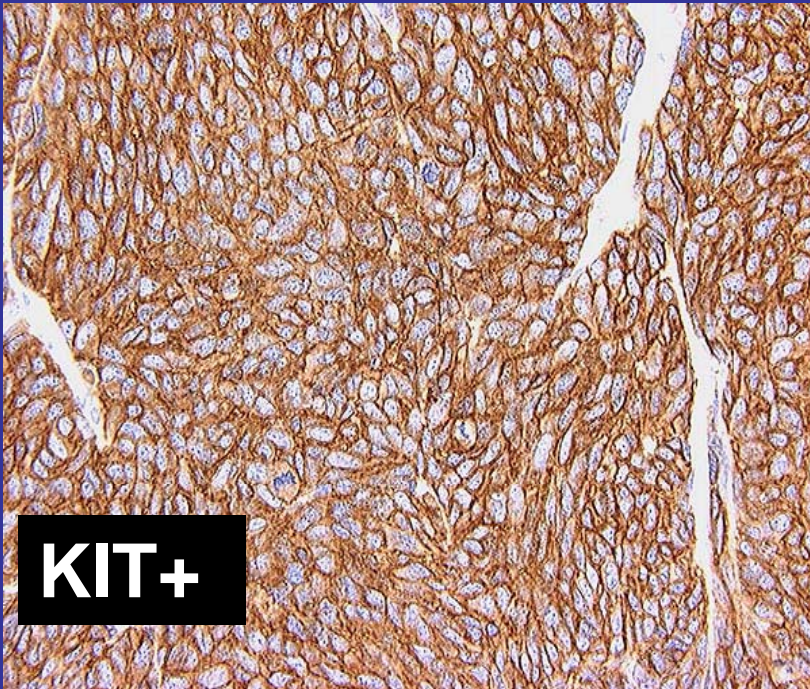
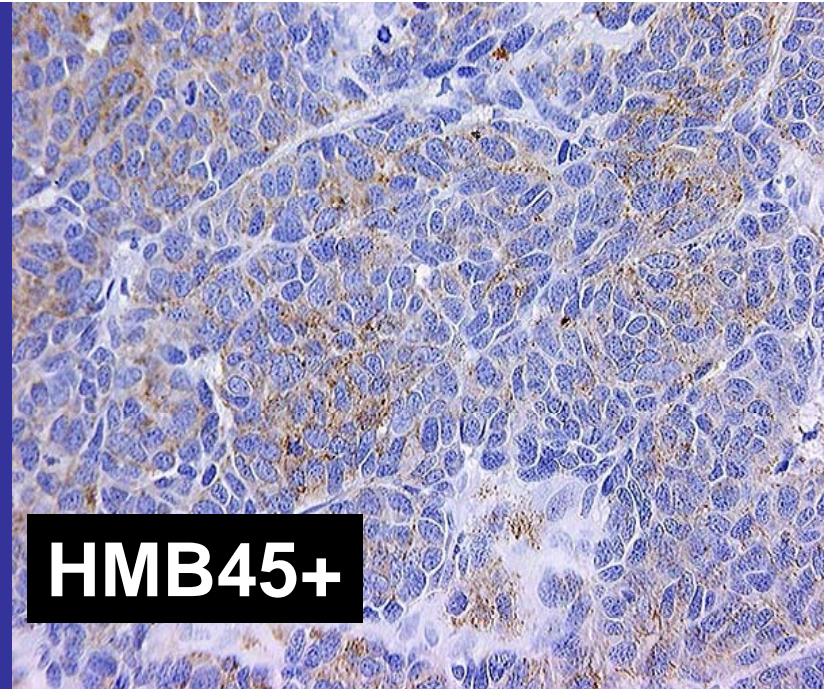
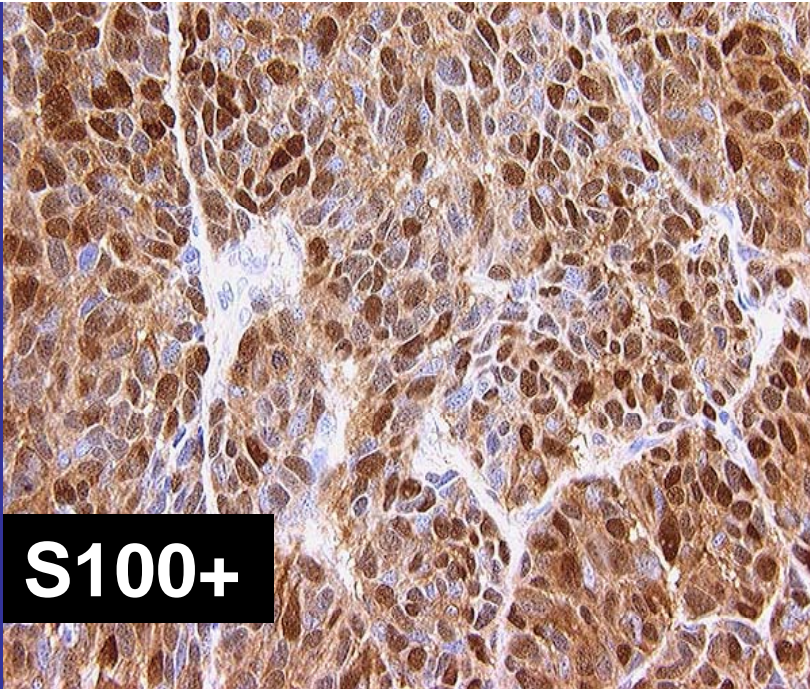








KIT+



METASTATIC MELANOMA

CAUTION: METASTATIC MELANOMA MAY CLINICALLY PRESENT AS A SINGLE INTRAMURAL MASS IN THE GI TRACT (particularly the small intestine).

MELANOMA CAN SHOW STRONG DIFFUSE KIT IMMUNOREACTIVITY.

MALIGNANT KIT+ SPINDLE CELL LESIONS IN THE GI TRACT ARE NOT ALL GISTS!

- Questions or Comments...
- Please email me..
 - her2007@columbia.edu
 - (all feedback welcome... negative or positive.. your input will help improve lectures less for next years medical students...)