

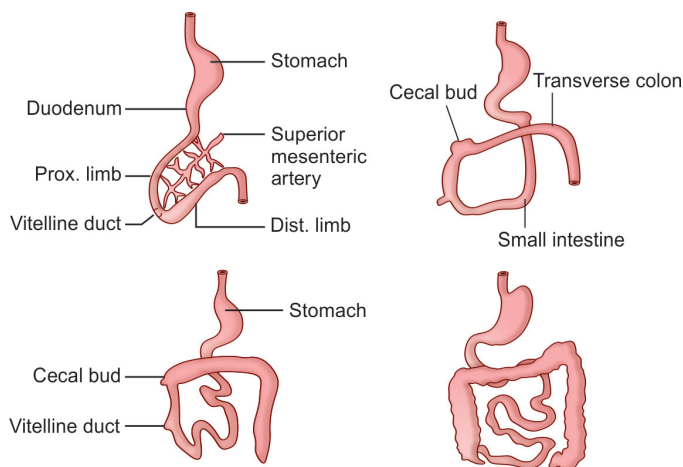
Small Intestine

7.1 ANATOMY

- **Largest endocrine organ**

Embryology

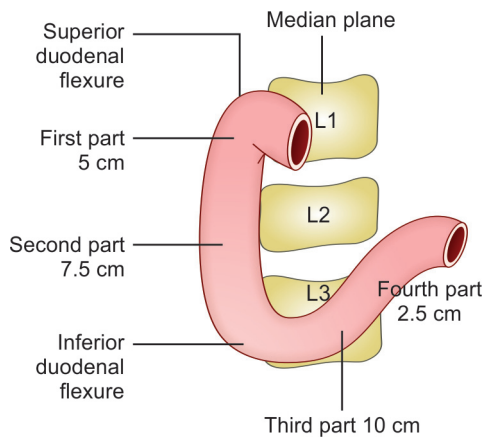
- Primitive gut is formed from endodermal lining, the yolk sac. Endodermal layer gives rise to epithelial lining of intestine
- Splanchnic mesoderm surrounding the endoderm form the muscular and all other layers of intestine, and also mesentery
- Nerves and neurons on the wall are derived from neural crest
- All small intestine is derived from midgut except duodenum
- Herniation of midgut occurs through umbilicus—5th week
- Loop divided by vitello intestinal duct into cranial and caudal
- Cranial limb form distal duodenum, jejunum, proximal ileum
- Caudal limb form distal ileum, cecum, ascending colon and proximal two-thirds of transverse colon
- Vitello intestinal duct—obliterates before birth
- In 2%—persist as Meckel's
- Endodermal proliferation causes occlusion of the lumen—5th week
- Mesodermal expansion and apoptosis of endoderm produces recanalization of tube starts at 7th week
- Recanalization—complete by 9th week
- Intestines return to abdominal cavity—by 10th week, undergo 270° rotation
- Jejunum placed in left upper quadrant
- Cecum enters last—initially RUQ and later shift to RLQ
- Primitive SI—lined by cuboidal cells
- Villi begin to form by 9th week—proceed caudally even in colon
- Crypt formation by 10–12th week
- Crypt layer—site of continual cell renewal
- **Crypt cells ascend and differentiate into 4 cell lines**
 - Absorptive enterocyte—95% on int cell population
 - Goblet cells
 - Paneth cells
 - Entero-endocrine



Small Intestine—Gross Anatomy

- Length—300–850 cm
- Duodenum—25 cm
- No demarcation between jejunum and ileum
- Proximal two-fifths represent jejunum, distal three-fifths—ileum “Shirt sleeve felt through a coat sleeve”—the feeling on palpating jejunal wall. This is due to the thick wall of jejunum, the mucus membrane can be felt through the muscle wall. The wall of ileum is thin, so feels as single layer.

Duodenum



- Root of mesentery attachment—to the posterior abdominal wall to the left of L2 obliquely to the right inferiorly to right SI joint
- Artery: SMA
- Veins follows
- Nerves—parasympathetic—through vagus—secretory function
- Sympathetic from plexus around SMA which causes pain

Characteristic	Jejunum	Ileum
Color	Deeper red	Paler pink
Caliber	2–4 cm	2–3 cm
Wall	Thick and heavy	Thin and light
Vascularity	Greater	Less
Vasa recta	Long	Short
Arcades	A few large loops	Many short loops
Fat in mesentery	Less	More
Circular fold (L. plica circulares)	Large, tall and closely packed	Low and sparse; absent in distal part

Microscopic Anatomy

- Serosa—consists of visceral peritoneum—single layer mesothelium
- Muscularis propria—outer longitudinal—thin, inner circular—thick
- Ganglion cells of myenteric plexus of Auerbach between muscle layers
- Submucosa—fibroelastic connective tissue
 - Contain vessels, lymphatics and nerves—Meissner's plexus
 - Strongest layer used for anastomosis
- Mucosa

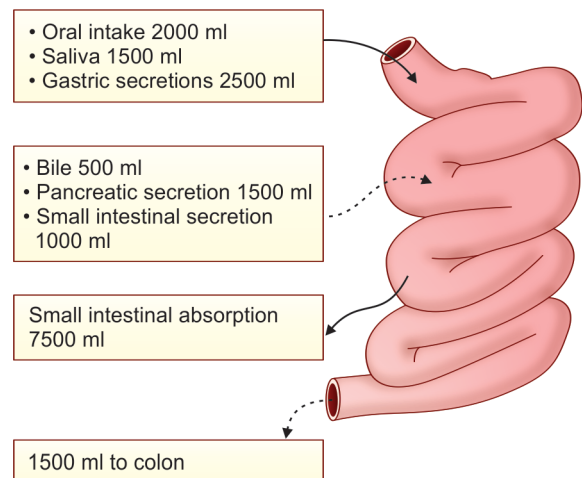
Muscularis mucosa

Lamina propria—connective tissue layer

- Contain plasma cells, macrophages, fibroblasts

- Protective role against microorganisms that penetrate the epithelium—immune function
- Plasma cells secrete—immunoglobulins
- **Epithelium**—continual sheet of cells
 - Crypt—main function is renewal,
 - Also exocrine and endocrine functions and water and ion secretion
 - Villous epithelium helps in digestion and absorption
- 4 cells in mucosa
 - Absorptive enterocytes
 - Goblet cells secrete mucin
 - Paneth cells—secrete lysozyme and cryptidins for defense
 - Entero-endocrine cells secrete GI hormones
- Villi—tallest near distal duodenum and proximal jejunum
 - Shortest—in distal ileum
- Absorptive enterocytes covered by microvilli—increase area by 30-fold
- Microvilli covered by fuzzy coat of glycoprotein—glycocalyx—further increase in absorptive area

Digestion and Absorption



- Liters of fluid and many hundreds of grams of food reach small intestine
- Stomach breaks down particles to 1 mm or smaller
- SI is primarily responsible for absorption of carbohydrates, fat and proteins, ions and water

Carbohydrates

- In Western diet—300–350 gm
- 50% starch, 30% sucrose, 6% lactose. Rest maltose, fructose, sorbitol, etc.

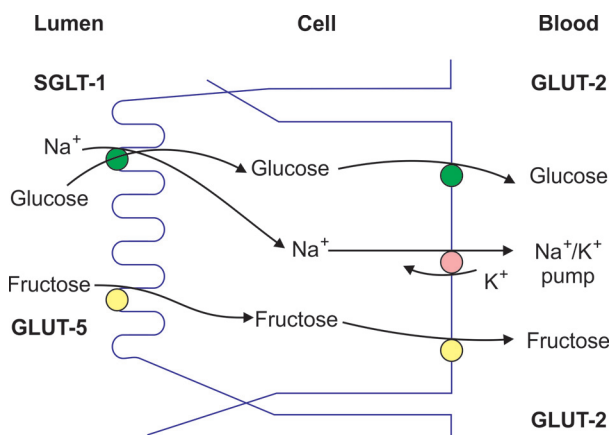
- Starch-polysaccharide with long chains of glucose. Starch contains amylose and amylopectin
 - Amylose—20%—amylase splits it into maltose and maltotriose
 - Amylopectin—80%—amylase splits this into maltose, maltotriose and residual branch saccharides (dextrins)
- Starch—almost totally converted to maltose and other polymers before they pass duodenum and proximal jejunum
- Remaining digestion by brush border enzymes

Carbohydrates: Brush Border Enzymes

- Split disaccharides to monosaccharides
- Glucose—>80% end product of digestion
- Galactose and fructose—10%

3 Transporter Systems

- Sodium-glucose transporter-1 (SGLT-1)
 - Co-transport with Na
 - It is an active transport
 - Glucose and galactose are transported
- Glucose transporter-5 (GLUT-5)
 - Not sodium or energy dependent
 - Fructose is transported
- GLUT-2: Located at basolateral membrane helps in exit of glucose from cytosol into intracellular space
- Transport across intestinal epithelium

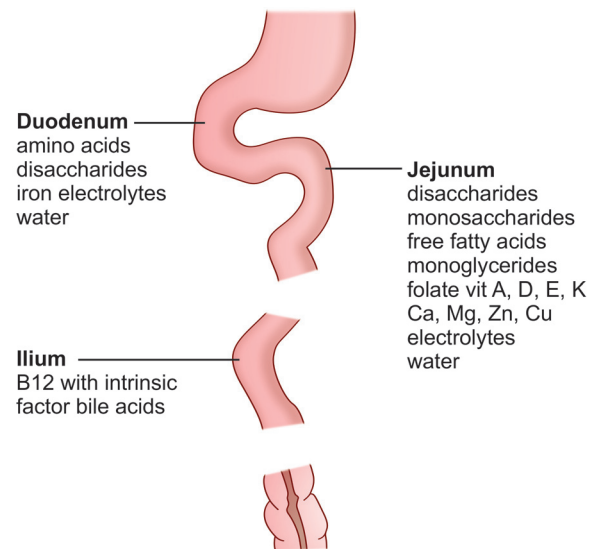


Protein

- Digestion is initiated in stomach—acid denatures protein
- Pancreatic trypsinogen is inactive. Duodenal brush border enzyme enterokinase—activate it to trypsin
- Activated trypsin—activate other enzymes like trypsin, elastase, chymotrypsin
- Produce peptides and smaller proteins which are acted upon by carboxy peptidases—split to produce di and tripeptides
- Absorbed by Na mediated active mechanism

- Peptidase enzymes in cells and brush border—further split and generate dipeptides and amino acids and pass into portal system
- 80–90% digestion and absorption completed in jejunum
- 70% absorbed as amino acids

Areas of Absorption



Endocrine Function of SI

- Function as endocrine, autocrine, paracrine and as neurotransmitters
- Signal through G protein—coupled group of receptors found in the body
- Other receptors
 - EGFR, IGFR, Fibroblast GFR, PDGFR
- Some peptides act as neurotransmitters

Immune Function

3 Areas

- Peyer's patches
 - Lamina propria lymphoid cells
- Intraepithelial lymphocytes

Peyer's Patches

- Unencapsulated lymphoid nodules—constitute the afferent limb of gut associated lymphoid tissue—contain microfold (M) cells—recognize antigens—activate B and T cells. Activated lymphocytes then migrate to lymph nodes and then to lamina propria.
- B lymphocytes become IgA
- 60% are T cells
- 40% B cells
- Major immune mechanism—IgA
- SI contains >70% of IgA producing cells in the body

- IgA is produced by plasma cells in lamina propria—secreted into intestine
- IgA—prevents bacterial colonization and adherence to epithelial cells
 - Neutralizes bacterial toxins
 - Neutralizes viral activity
 - Blocks absorption of antigens from gut
- IgA—does not destroy infective organisms or antigens

7.2 SMALL BOWEL NEOPLASMS

- Small bowel—75% of length and 90% surface area of GIT
- Both benign and malignant tumors are rare
- Can arise from epithelium, neural tissues, lymphatics and mesenchymal cells or metastases
- Number of LNs to be examined for optimum staging
 - Nonampullary duodenal ca—5 LNs
 - SI cancer—at least 9 LN

Epidemiology

- <5% of GI tumors are small intestinal
- <2% of malignant GI tumors
- 5-year survival is 80%—with local disease
 - With regional and distal metastasis—survival reduces
- Benign are asymptomatic and most are distally located
- Among symptomatic cases—75% are malignant
- More than 40 histological types are present in malignant, 95% are either adenocarcinoma, carcinoid, lymphoma or GIST.
- Most common benign tumors—stromal tumors and adenoma
- Benign more common in distal SI
- Most common malignant tumor—adenocarcinoma constitute 30–50% of malignant SI tumors
- NET—25 to 30%
- Adenocarcinoma more common in proximal SI
- Other malignant tumors more common—distal SI

Protective factors

- High levels of benzopyrene hydroxylase + folate receptors
- Low bacterial load
- Fast transit time
- High cellular turnover
- Liquid and alkaline medium
- Safe stem cells
- Immune protection—IgA

Risk factors

- FAP
- HNPCC
- Peutz-Jeghers syndrome
- MUTYH associated polyposis
- Other genetic conditions: Gardner syndrome, von Recklinghausen syndromes, cystic fibrosis
- Crohn's disease
- Celiac disease
- Immunosuppression
- Other malignancies
- Smoking
- Alcohol (>80 g/day)
- Red meat
- Salted food

Genetics

- KRAS
- APC gene (5q)
- P53 (17q)
- DCC (18q)
- DPC4 (SMAD4)
- MSI-H—associated with celiac disease—CpG methylation—links celiac disease to cancer

Clinical Features

- Usually vague
- Anorexia, dyspepsia
- Pain abdomen—due to obstruction—most common symptom—intussusception in benign
- Bleeding next common—hematochezia or hematemesis
- Most are asymptomatic

Diagnosis

- Need high index of suspicion
- Correct preop diagnosis made only in 50% of symptomatic
- Upper GI series with follow through—diagnosis in 50–80% of malignant tumors
- CT enteroclysis has 95% accuracy
- MRI enteroclysis has 98% sensitive and 97% specific
- UGI scopy and colonoscopy
- Enteroscopy—push type

- Double balloon enteroscopy can be done. With this, preoperative tattooing can be done and is associated with high rate of perforation
- X-ray abdomen is useful in obstruction
- CT abdomen can detect extraluminal tumors and help in staging
- Angiography useful in vascular tumors

Benign Tumors

- Most common tumors reported in autopsy—adenomas
- Most common benign tumors producing symptoms—stromal tumors
- When a benign tumor is encountered at surgery—resection is warranted—may become symptomatic

Stromal Tumors

- Arise from interstitial cells of Cajal
- 3 histological types: Fusiform (77%), epithelioid (8%) or mixed (15%)
- Express CD 117 (c-kit proto-oncogene)—>95%
 - CD 34 in 70–90%
- Stain +ve for actin, desmin, S100
- Equal in both sexes
- Firm gray white, with whorled appearance on cut section

Treatment

- Surgical resection
- Most common indication or surgery in benign—bleeding

Adenomas

Spigelmann Classification Refer Colorectal Chapter

- 3 types—true adenomas, villous, Brunner gland adenomas
- Adenomas are seen, ileum 50%, jejunum 30%, duodenum 20%
- Mostly single and asymptomatic
- Most common symptom—bleeding/obstruction.
- Villous adenomas—most common site—duodenum—associated with FAP
- Villous and true adenomas are premalignant. Adenoma—carcinoma sequence—related to size >5 cm
- Malignant potential 35–55%

Treatment

- Resection in ileum and jejunum
 - Duodenum—endoscopic resection and can cause more bleeding perforation

- If there are recurrence/invasive features—pancreaticoduodenectomy

- Endoscopic mucosal resection

In FAP

- Duodenal adenomas found in 50–90%
- Increasing age—-independent risk factor
- FAP carry 5% lifetime risk of duodenal adenocarcinoma

Brunner Gland Adenoma

- Benign hyperplastic lesions arising from Brunner glands of proximal duodenum
- Symptoms mimic peptic ulcer disease
- Endoscopic diagnosis
- Treatment—excision—endoscopic/surgical
- No malignant potential

Lipoma

- Common in ileum
- Single, intramural lesion in submucosa
- 6th–7th decade
- More common in males
- Only less than one-third are symptomatic
- Most common manifestation—obstruction and bleeding
- No malignant potential
- Treatment—excision only if resection is simple

Peutz-Jeghers Syndrome

- Autosomal dominant inheritance
- Mutation of STK11 gene (LKB1) tumor suppressor gene
- Mucocutaneous melanosis over circumoral, palms, soles, digits, perianal region
- Intestinal hamartomatous polyps—entire jejunum and ileum—most common
- 50% have colorectal and 25% gastric lesions
- Abdominal pain due to intussusception—most common presentation
- Bleeding manifest as anemia—due to autoamputation of polyps
- Extracolonic cancers occur in 50–90% (SI, pancreas, stomach, lung, uterus)
- Resection of only the affected segment—no extensive resection needed
- Not curable

Hemangioma

- Developmental malformation—submucosal proliferation of blood vessels
- Most common—in jejunum
- 3–4% of all benign tumors, 60% are multiple

Associated with

- Osler-Weber-Rendu disease
- Turner syndrome—cavernous haemangiomas of intestine
- Most common symptom—bleeding
- Angiogram and Tc 99m RBC scanning—localise—resection warranted
- Localised also by intraoperative transillumination and palpation

MALIGNANT TUMORS

<i>Tumor type</i>	<i>Cell of origin</i>	<i>Frequency</i>	<i>Predominant site</i>
Adenocarcinoma	Epithelial cell	36–50%	Duodenum
Carcinoid	Enterochromaffin cell	20–40%	Ileum
Lymphoma	Lymphocyte	12–15%	Ileum
GIST	Interstitial cell of Cajal	10–15%	

Diagnosis

- X-ray, small bowel follow through
- CT
- Double balloon enteroscopy
- Video capsule enteroscopy
- Octreotide scan
- Tc 99 radionuclide scan
- There is an increase in incidence of NETs

Clinical Features

- Almost always produce symptoms—most common pain and weight loss
- Obstruction in 15–35%—due to infiltration and adhesions vs intussusception in benign
- Diarrhea with mucus and tenesmus
- Bleeding with anemia—more in GIST
- Palpable mass in 10–20%
- Perforation in 10%—usually in lymphomas and sarcomas

NET

- Arise from enterochromaffin cells (Kulchitsky) cells from neural crest situated at base of crypts of Lieberkuhn-Argentaffin cells
- Foregut-respiratory tract, thymus-secrete-low serotonin, more 5 HTP (hydroxytryptophan) or ACTH
- Midgut—high serotonin
- Hindgut—serotonin and somatostatin and peptide YY
- Most common site—appendix (most common) and GIT

Carcinoid Syndrome

- In liver metastasis
- Direct secretion into venous system bypassing portal system—lung, ovary

NET-Pathology

- 70–80% asymptomatic
- Appendiceal NET—only 3% metastasis, ileal NET—35% metastasis
- Size <1 cm—associated with 2% metastasis
- Size 1–2 cm—50% metastasis
- >2 cm—80–90% metastasis
- Submucosal lesions—yellow on cut surface
- Seen on antimesenteric border of SI—associated with larger mesenteric mass of LN with desmoplastic reaction—mistaken for primary
- Produce kinking—obstruction
- Multicentric in 20–30% (mostly any GIT malignancy)
- Synchronous adenocarcinoma in colon—in 10–20%
- MEN 1 association in 10%

Clinical Features

- Most common—abdomen pain—due to obstruction-desmoplastic reaction due to humoral agents and intussusception
- Diarrhea—due to partial obstruction and may be secretory and causes weight loss
- Mesenteric nodes cause venous engorgement and ischemia

Malignant Carcinoid Syndrome

- In <10% of NET
- Usually from GIT—SI carcinoid with hepatic metastasis
- Also from bronchus, pancreas, ovary—extra abdominal disease without liver metastasis
- Manifestations—cardiac
 - Vasomotor
 - GIT
- Substances responsible—serotonin, 5HTP, histamine, dopamine, substance P, PG

Clinical Features

- Cutaneous flushing (80%)
- 4 types
 - Diffuse erythematous short lived, on face neck
 - Violaceous associated with longer duration with permanent cyanotic flush, injected conjunctiva
 - Prolonged flushes may last 2–3 days and with lacrimation
 - Bright red patchy flushing—typically seen in gastric NET

- Hepatomegaly (76%)
- Right-sided valvular heart disease (40–70%)
- Asthma—25%—due to serotonin and bradykinin
- Diarrhea
 - Episodic after a meal, watery, explosive
 - Serotonin—responsible
- Cardiac—mainly right side of heart
 - In 15% left side of heart
 - Most common—pulmonary stenosis (90%)
 - Tricuspid insufficiency (47%)
 - TS (42%)
- Malabsorption and pellagra (dermatitis, dementia, diarrhea—3Ds)—due to diversion of dietary tryptophan

Diagnosis: NET

- Elevated humoral factors—basis of diagnosis
- Serotonin—in liver and lung converted into 5 HIAA
 - 24-hour urine 5 HIAA—highly specific—not sensitive
 - CgA-Sp 95%, sensitivity 55%
 - Combined CgA and 2-hour urine 5HIAA
 - Combined CgA and N-terminal probrain natriuretic peptide (NT-proBNP)
- Measurement of serotonin, substance P, neurokinin A—not reliable

Imaging

- Barium studies
- CT—solid mass with surrounding strands, kinking of bowel
- MRI—in liver metastasis
- Indium labelled 111 petetreotide—binds to somatostatin 2 and 5 receptors
- PET CT—only useful in high grade
- Ga-DOTATATE PET/CT is the choice for localizing and in metastasis

NET: Treatment

Surgery

- Based on site, size and metastasis
- <1 cm without regional LN metastasis—segmental resection
- >1 cm, multiple or with LN metastasis, regardless of size—wide excision of bowel and mesentery

- Terminal ileum—right hemicolectomy
- Explore for multicentric lesions
- Anaesthesia can precipitate carcinoid crisis—manifested as hypotension, bronchospasm, flushing, arrhythmias and treated with IV octreotide 50 to 100 µg bolus—infusion 50 µm/hr

In Liver Metastasis

- Surgery
- TACE, TARE
- Liver transplant

Adenocarcinoma

- 50% of malignant tumors of SI
- M>F
- More common in duodenum and jejunum
- Associated with Crohn's disease—more common in ileum
- Vague presentation—pain, weight loss

Treatment

Surgery

- If tumor invasion to adjacent structures present NACT—surgery after 2–3 months
- Radical resection with lymphadenectomy
- Pancreaticoduodenectomy, right hemicolectomy—depending on lesion site

Postop Chemo

- In poorly differentiated
- If <10 LN sampled
- In metastatic—FOLFOX—first line, FOLFIRI—second line
 - **Duodenal adenomas**—<1 cm endoscopic removal
- >2 cm—surgical—pancreaticoduodenectomy (PD) if involving D2
- 1–2 cm—EUS—if in mucosa—endoscopic removal and follow-up
- In FAP—surveillance endoscopy—endoscopic removal—if surgery needed—standard PD

Metastatic Tumors

- More common than primary
- Most common from—cervix, ovary, kidney, stomach, pancreas, colon
- By direct extension or implantation
- Extra-abdominal malignancy—most common—melanoma