Section 9

LECTURE

Pathology of the Intestines
VASCULAR AND INFLAMMATORY DISEASES
OF THE INTESTINES

GENERAL OUTLINE:

VASCULAR DISORDERS

I. VASCULAR MALFORMATIONS AND ANOMALIES
   Vascular etasias
   Sporadic vascular etasias
      - colon (angiodysplasia)
      - stomach (watermelon stomach)
   Hereditary vascular etasias
      - hereditary hemorrhagic telangiectasia (Osler-Webber-Rendu disease)
   Arteriovenous malformations

II. VASCULITIS
    Small vessel vasculitis
    - Henoch-Schönlein purpura
    - Microscopic polyangiitis
    - Vasculitis secondary to multisystem autoimmune disease
    Large vessel vasculitis
    - Polyarteritis nodosa

III. NON-VASCULITIC ISCHEMIC DISEASE
     Occlusive disease
     - Arterial occlusion
     - Venous occlusion
     - Bowel strangulation
     Nonocclusive disorders
     - Systemic hemodynamic disturbances
     - Local hemodynamic disturbances

IV. VASCULAR MANIFESTATIONS OF SYSTEMIC DISEASES
    Amyloidosis

V. VARICES

INFLAMMATORY DISORDERS

I. INFLAMMATORY DISORDERS WITH SPECIFIC ETIOLOGIES
   Infectious enterocolitis
   "Immune-mediated" enteropathy
   Diverticular disease

II. IDIOPATHIC INFLAMMATORY BOWEL DISEASE
    Crohn's disease
    Ulcerative colitis
VASCULAR DISORDERS OF THE INTESTINES

I. VASCULAR MALFORMATIONS AND ANOMALIES

Vascular malformations of the gastrointestinal tract are being recognized increasingly as a major cause of both acute and chronic gastrointestinal bleeding. In the small intestine, they are the most common cause of bleeding. Increased recognition of their importance has been a direct result of the development of techniques permitting their visualization, such as selective mesenteric angiographic and colonoscopic examination.

The most important intestinal vascular anomalies are:
- Vascular ectasias or telangiectasias
- Arteriovenous malformations
- Systemic connective-tissue disorders affecting blood vessels

A. VASCULAR ECTASIAS

1. Sporadic Vascular Ectasias (Telangiectasias)

Vascular ectasias consist of clusters of tortuous thin-walled vessels (resembling venules and/or capillaries), often lined only by endothelium and lacking either muscle or adventitia, located exclusively in the mucosa and submucosa. Sporadic telangiectasias are the most common vascular anomalies of the GI tract. They are thought to be acquired abnormalities of vessel structure (possibly related to low-grade obstruction of submucosal veins). They usually present with GI bleeding that is recurrent and low grade but is occasionally massive. Although these lesions are sometimes treated by electrocoagulation, segmental resection may be required for uncontrolled bleeding.

The most common type of acquired vascular ectasia is that which occurs in the colon of individuals over the age of 50 (also known as angiodysplasias or incorrectly as arteriovenous malformations). These ectasias usually occur in the cecum or proximal ascending colon and account for nearly 40% of all colonic vascular lesions. Specifically, they are the most common vascular anomaly of the GI tract and the most frequent cause of lower GI bleeding in individuals over the age of 60. Like other ectasias, they usually produce recurrent low grade bleeding, but bleeding may be massive and require surgical resection (right ileocolectomy).

2. Hereditary Vascular Ectasia

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Webber-Rendu disease, is a systemic disorder of blood vessels characterized by multiple small aneurysmal telangiectases primarily involving the skin and mucous membranes but often, or even solely involving the GI tract. In the GI tract, mucosal involvement is seen as multiple small red macules, but involvement may be transmural. The telangiectasias appear microscopically as blood-filled lacunae that may be part of extensive plexuses of

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1 Ectasia literally means dilatation, expansion, or distention. Telangiectasia is a more specific term that refers to ectasia of a distal (tele-) vessel (angeion). In other words, telangiectasia is a compound word that means small vessel ectasia.

2 Although the term dysplasia is commonly used in the context of cytological abnormalities related to neoplasia, the word dysplasia literally means "abnormal development." Angiodysplasia is therefore a compound term that refers to abnormal development of vessels, and has nothing to do with cytological abnormalities or neoplasia.
extremely thin-walled ectactic vessels that primarily involved the muscularis mucosae and superficial submucosa.

The characteristic telangiectasias are thought to originate from capillaries or post-capillary venules and represent direct connections between arteries and veins. The walls of these vessels typically consist solely of an endothelium with a continuous basement membrane and lack both smooth muscle and elastic fibers. The vessels have little, if any, perivascular connective tissue intrinsic to their structure and, thus, will bleed readily if the tissue within which they occur does not offer secondary stromal support. Thus, telangiectasias in the nasal or gastrointestinal mucosa bleed more readily than those in the dermis.

Although it is an autosomal dominant disorder, as many as 20% of patients have a negative family history. After epistaxis, which occurs in 80% of affected individuals, gastrointestinal bleeding is the most frequent presentation of HHT and occurs in 10% to 40% of cases.

The pathogenesis of HHT has not yet been fully elucidated, but genetic studies have shown that HHT is actually a family of disorders caused by mutations in various genes. Recently, mutation of the gene (located at chromosome 9q3), for endoglin, the most abundant transforming growth factor β (TGF-β)-binding protein on endothelial cell membrane surfaces, has been identified as a specific molecular abnormality in one form of HHT.

3. Secondary Vascular Ectasias

Vascular ectasia in the GI tract may also occur as a secondary consequence of some systemic disorders. Vascular ectasia is sometimes associated with renal failure, cirrhosis with portal hypertension, systemic sclerosis (especially the CREST syndrome: T = telangiectasias), von Willebrand’s disease, aortic stenosis, or radiation-induced hypervascularity. The lesions in all of these disorders are histopathologically indistinguishable from those of the sporadic forms of vascular ectasia.

B. ARTERIOVENOUS MALFORMATIONS

The term arteriovenous malformation (AVM) refers to vascular lesions consisting of focal meshworks of large thick-walled veins that are usually associated with arteries and capillaries and are structurally abnormal. True AVMs may be distributed throughout all layers of the bowel wall, rather than being limited to the mucosa and submucosa like most small vessel ectasias. However, most AVMs are submucosal and less than 5 mm in diameter.

AVMs may occur in patients of any age and may involve any segment of the gastrointestinal tract. Reports of AVMs in children and young adults have raised the possibility that at least some of the lesions are congenital.

Disorders of connective tissue that affect blood vessels such as pseudoxanthoma elasticum and the Ehlers-Danlos syndrome may also cause vascular weakening with spontaneous rupture of vessels and/or be associated with vascular malformations in the GI tract.
II. VASCULITIS

A. SMALL VESSEL VASCULITIS

1. Henoch-Schönlein Purpura

Necrotizing small-vessel vasculitis involving the bowel mucosa but sparing the larger vessels of the mesentery is characteristic of Henoch-Schönlein purpura (HSP), a distinctive form of hypersensitivity vasculitis. Targeting of small vessels as opposed to medium-sized muscular arteries distinguishes HSP from polyarteritis nodosa, the two kinds of vasculitis in which the gastrointestinal tract is usually involved.

Henoch-Schönlein purpura is a multisystem disorder characterized by leukocytoclastic vasculitis with a characteristic clinical picture that includes palpable purpura, typically on the lower extremities, with involvement of the gastrointestinal tract and kidneys in addition to joints. Histopathologically, a necrotizing vasculitis of small vessels, both arterial and venous is seen. This pattern of vascular injury is seen in all of the distinct syndromes encompassed by the broader classification of hypersensitivity vasculitis, including microscopic polyangiitis (microscopic polyarteritis), serum sickness, essential mixed cryoglobulinemia, vasculitis associated with connective-tissue diseases, and vasculitis associated with malignant tumors, as well as septic vasculitis or septic embolism. However, HSP can be readily distinguished from all of these by the pathognomonic finding IgA and C3 deposition in vessel walls.

The pathogenesis of HSP is related to vascular entrapment of circulating IgA immune complexes with the activation of complement. The presence of IgA, C3 and fibrinogen in combination with the relative absence of other immunoreactants distinguishes HSP from other forms of necrotizing vasculitis, which typically have vascular deposits of IgG, IgM, and early complement components.

A number of drugs have been implicated in the genesis of the IgA-generating immune response in HSP, including aspirin, phenacetin, penicillin, tetracycline, erythromycin, quinidine, and thiazide diuretics. Other forms of antigenic stimulation implicated in the genesis of the immune response in HSP have included respiratory tract infections, insect stings, and immunizations. In many cases, however, no causal factor can be found.

The prognosis of HSP is generally good, and the treatment usually consists of supportive and symptomatic therapy until the disease resolves. Although the vasculitis in this syndrome has a remarkable tendency to resolve and recur many times during the weeks or months after the initial presentation, spontaneous resolution usually occurs.

2. Microscopic Polyangiitis

Microscopic polyangiitis may involve the intestine to produce severe inflammatory infiltration of arterioles, capillaries, and venules with fibrinoid necrosis. The necrotizing vasculitis may involve larger vessels as well. The diagnosis of microscopic polyangiitis requires few or no immune deposits in the affected vessels (“pauci-immune vasculitis”). The disease is often drug-induced (formerly known as hypersensitivity vasculitis) from such compounds as allopurinol, indocin, ampicillin, penicillins, tetracyclines, chloramphenicol, sulfonamides, diazepam, isoniazid, spironolactone, griseofulvin, and trimethadone. This type of vasculitis is associated with antineutrophil cytoplasmic antibodies (ANCA).

ANCA directed against antiproteinase 3 is known as c-ANCA and is highly specific for Wegener’s granulomatosis (another specific cause of small-to-large vessel vasculitis that may involve the GI tract).
ANCAs directed against various cytoplasmic proteins such as myeloperoxidase, elastase, and lysozyme are known as p-ANCAs and are seen in microscopic polyangiitis as well as vasculitis in the Churg-Strauss syndrome (see below), inflammatory bowel disease, and paraneoplastic syndromes.

3. Vasculitis Secondary to Multisystem Autoimmune Disease

The vasculitides associated with systemic lupus erythematosus (SLE), dermatomyositis, and rheumatoid arthritis (RA) may all affect the GI tract. Fibrinoid necrosis of arterioles, capillaries and venules with perivascular lymphocytic inflammation is seen. These vasculitides usually have immune complexes (not IgA) in the vessel walls. Since immune complexes are also seen in association with essential mixed cryoglobulinemia, some drug-induced vasculitis, and some infection-associated vasculitis, these disorders are included in the differential diagnosis of small vessel immune-complex vasculitis.

B. LARGE VESSEL VASCULITIS

1. Polyarteritis Nodosa

Polyarteritis nodosa (PAN), a generalized segmental arteritis of small and medium-sized muscular arteries (but no involvement of arterioles, capillaries or venules), involves the GI tract in 50% to 66% of cases. GI involvement rarely occurs in the absence of renal involvement, so it is helpful to know whether or not the patient has hematuria. Classically, GI involvement targets the mesenteric arteries and produces a characteristic nodular or beaded appearance of the affected vessels on angiography. The manifestations of GI involvement by PAN are highly variable and relate to the ischemia produced by the affected vessel(s).

Microscopically, PAN is characterized by fibrinoid necrosis of the vessel wall which may or may not be circumferential in distribution. The mural elastic fibers show fragmentation on elastic tissue stains. Damage to the elastic network of the arterial wall may lead to aneurysm formation. With intimal damage, thrombosis ensues.

III. MESENTERIC VASCULAR INSUFFICIENCY

Non-vasculitic causes of intestinal ischemia encompass processes that produce mesenteric vascular insufficiency such as:
- mesenteric artery atherosclerosis
- thrombosis of the mesenteric artery of the mesenteric vein
- embolism

In the presence of chronic non-obstructive compromise of mesenteric blood flow, a superimposed low-flow state may be the critical event in precipitating bowel infarction. Acute ischemia produces GI bleeding that, depending on the cause, severity and duration of the problem, may progress to bowel perforation (if transmural necrosis occurs). Thus, prompt diagnosis and surgical resection of the affected bowel segment are critical in cases of total vascular occlusion. Chronic ischemia (chronic) may cause nonspecific abdominal pain, abdominal angina (abdominal pain 10-15 min after eating) or may mimic inflammatory bowel disease.

Ischemic disease of the esophagus and stomach are rare, presumably because of the multiple sources of blood supply and collateral circulation. Acute ischemia of the small intestine and/or colon is most frequently (50% of cases) caused by non-obstructive mesenteric ischemia: i.e., a low flow state (eg,
myocardial infarction or atrial fibrillation) is superimposed on severe atherosclerotic stenosis of the proximal mesenteric vessels. Thus, acute ischemic disease is most common in the elderly, especially in patients with atherosclerosis and cardiovascular disease.

The other major causes of intestinal ischemia, that together with non-occlusive mesenteric ischemia account for 95% of all acute intestinal ischemia, are superior mesenteric artery (SMA) embolism, SMA thrombosis, and mesenteric vein thrombosis (in decreasing order of frequency).

1. Vaso-Occlusive Disease

Mesenteric arterial occlusion is most often caused by embolism. Approximately 75% of acute mesenteric infarction are caused by embolism and the majority of those cases result from cardiac mural thrombosis following myocardial infarction. Atheroembolism is especially common following arterial surgery such as abdominal aortic aneurysm repair. Patients usually present with severe abrupt-onset abdominal pain and spontaneous GI emptying (bloody vomiting and diarrhea).

Immediate surgical intervention is required to re-establish arterial flow by embolectomy and to resect non-viable bowel before gangrene and perforation occurs (1 to 4 days post-occlusion). Mortality ranges from 50-90%. Bowel infarction from acute mesenteric arterial thrombosis usually occurs at the site of a pre-existing arterial defect such as an atherosclerotic plaque or an anatomic anomaly and frequently occurs in the setting of a low-flow state.

Depending on the duration of the ischemia, the resected bowel may appear red and grossly hemorrhagic transmurally or blackened and gangrenous. The lumen may be blood-filled and pseudomembranes may cover the mucosal surface.

Mesenteric vein thrombosis accounts for 5-15% of mesenteric ischemia. It is idiopathic in half of cases. In the remaining cases, predisposing factors that cause venous thrombosis can be identified such as cirrhosis, congestive splenomegaly, hypercoagulable states (eg, pregnancy, estrogen/oral contraceptive steroid use, migratory thrombophlebitis, antithrombin III deficiency, thrombocytosis, polycythemia vera, protein S or C deficiency, peripheral deep vein thrombosis), abdominal or intestinal inflammation (eg, peritonitis, pelvic abscess, inflammatory bowel disease, diverticular disease), or trauma (surgical or nonsurgical). Onset is usually insidious with vague nonspecific symptoms that may include abdominal pain and bloody diarrhea.

Bowel strangulation of any cause (volvulus, incarcerated hernia) will cause mechanical occlusion of mesenteric vessels that produces pathologic changes identical to those of either arterial or venous occlusion discussed above. Definitive diagnosis is possible only by clinicopathologic correlation.

2. Nonocclusive Vascular Disorders

Non-occlusive vascular disorders of the mesenteric or mural vasculature typically produce a patchy pattern of ischemic damage that is typically less severe than that produced by occlusive processes and less frequently requires surgical intervention.

Systemic hemodynamic disturbances such as administration of hypotensive and hypovolemic agents (eg, diuretics, digoxin, alpha-adrenergic blockers) or vasoconstricting drugs (eg, vasopression, ergot, cocaine) may lead to mesenteric arterial insufficiency.

Local hemodynamic disturbances from inflammation, trauma, or increased intraluminal pressure may also compromise blood supply, but these problems are usually clinically obvious, if not dramatic.
Ischemic colitis is most frequently related to non-obstructive disease. Most cases of ischemic colitis are mild and transient. Mucosal ischemia of the colon may be diagnosed by colonoscopic biopsy, and medical treatment of the underlying problem instituted. Important differential diagnoses include infections by toxin-producing organisms such enterohemorrhagic E. coli that produce a histologic picture of tissue ischemia but require immediate specific therapy.

IV. VASCULAR MANIFESTATIONS OF SYSTEMIC DISEASES

1. Amyloidosis

GI involvement is common in all types of systemic amyloidosis, occurring in more than 50% of all cases. Vascular infiltration by amyloid may produce a variety of lesions ranging from petechial hemorrhages of the mucosa to hemorrhage, ulceration, and inflammatory lesions mimicking inflammatory bowel disease. Congo red stain is required for diagnosis, and immunohistochemical studies may elucidate the composition of the amyloid fibrils (immune/light chain vs. non-immune protein).

V. VARICES

Bleeding from varices in the GI tract usually occurs from esophageal or gastric varices caused by portal hypertension. Colonic varices are also related to portal hypertension in most cases. Occasionally varices are treated by surgical resection or endoscopic banding. Involved veins are markedly ectatic and show variable amounts of mural fibrosis and luminal thrombosis.
INFLAMMATORY DISORDERS OF THE INTESTINES

I. INFLAMMATORY DISORDERS WITH SPECIFIC ETIOLOGIES

A. SMALL INTESTINE

a. Infectious enteritis: Most common GI problem, bar none, worldwide
   - A host of viral, bacterial, protozoal and nematode (rarely, fungus) pathogens can infect the small bowel of immunocompetent individuals
   - The GI tract is also a common place for opportunistic infection in the immunocompromised
   - All infections produce diarrhea and some produce malabsorption, depending on the type of injury
   - Degree of mucosal injury is largely a function of the virulence (invasive and destructive potential) of the organism
   - Diagnosis most often made by stool culture for enteric pathogens, viral culture, or stool examination for ova and parasites ("O&P" exam); Some organisms can be visualized by endoscopic biopsy
   - Organisms only rarely produce a pathognomonic pattern of injury; Culture usually required for definitive Dx and differentiation from Crohn's disease

Mechanisms of injury by organisms:

1. Toxin Production (watery diarrhea): *V. cholerae*; toxigenic *E. coli*; "Food poisoning" caused by toxins produced by staphylococcus or clostridia
2. Tissue Invasion (purulent or bloody diarrhea):
   - Bacteria- *Salmonella sp.*, *Shigella*, *Campylobacter jejuni*, *Yersinia enterocolitica*, *M. tuberculosis*, *M. avium intracellulare* (AIDS patients)
   - Protozoa- Opportunistic coccidia (cryptosporidium; isospora; microsporidia)
   - Worms- Strongyloides; toxocara (visceral larva migrans); hookworm
   - Viruses- Opportunistic (HSV and CMV) viruses
   - Fungi- Histoplasma; candida or aspergillus in immunosuppressed
3. Lumen dwellers (Mechanisms of injury vary):
   - Protozoa- Giardia lamblia
   - Worms- Ascaris; Trichuris (whipworm); Enterobias (pinworm)

b. Immunological disorders-

1. Celiac sprue (gluten enteropathy):
   - Characterized by complete flattening of the villi, diffuse absorptive cell injury,
     lymphoplasmacytic mucosal infiltration, crypt hyperplasia (all non-specific); progresses proximal (duodenum) to distal (jejunum ileum)
   - Definitive diagnosis and therapy both accomplished by a gluten (wheat)-free diet (prompt clinical response but histopathological injury slower to reverse - heals distal to proximal)
   - Complications include:
     a) Refractory sprue (requires steroid Rx);
     b) Collagenous sprue (mucosal collagen deposition);
     c) Hypop gammaglobulinemic sprue (mucosal plasma cells absent);
     d) Lymphoma

2. Immunodeficiency disorders causing malabsorption:
(a) Congenital agammaglobulinemia: Absence of plasma cells in mucosa
(b) Late-onset hypogammaglobulinemia (adults): paucity or absence of mucosal plasma cells; associated with giardiasis in many patients; may be accompanied by diffuse nodular lymphoid hyperplasia
(c) Selective IgA deficiency: Variable mucosal injury (normal to severe); lots of IgM and IgG plasma cells in mucosa

(3) Nodular lymphoid hyperplasia: Without hypogammaglobulinemia; Spontaneous regression without Rx is usual; Rare transformation to lymphoma reported

(4) Eosinophilic gastroenteritis: Hypersensitivity disorders in which the antigen is unknown; Eosinophilic infiltrates present in both bowel and peripheral blood

B. COLON

a. Infectious colitis:
   - Many of the same pathogens that infect the small bowel, also involve the colon (hence, "enterocolitis").
   - Some pathogens involve the colon alone: e.g., *Clostridium difficile* (antibiotic-associated pseudomembranous colitis); *Entamoeba histolytica*, *Schistosoma mansoni* or *japonicum*.
   - Colonic infections produce diarrhea but NOT malabsorption.
   - As in the small bowel, degree of mucosal injury is largely a function of the virulence (invasive and destructive potential) of the organism.
   - Diagnosis most often made by stool culture for enteric pathogens, viral culture, or stool examination for ova and parasites ("O&P" exam); some organisms can be visualized by endoscopic biopsy.
   - Organisms only rarely produce a pathognomonic pattern of injury. Culture usually required for definitive diagnosis and differentiation from Crohn's disease.

b. Immunological disorders: Eosinophilic enterocolitis

c. Diverticular Disease
   - Diverticulosis coli is the most common form of diverticular disease in the GI tract
   - "Acquired type" of diverticula consisting of mucosal and submucosal outpouchings through the muscularis propria at "weak" points where vessels penetrate the muscle; in contrast to congenital diverticula, these do not have a muscularis propria
   - Pathogenesis is debated (relationship to low fiber diet, hyperactive peristalsis and increased intraluminal pressure)
   - Fecal impaction and bacterial overgrowth can produce inflammation (diverticulitis) that may be complicated by bleeding or perforation with subsequent formation of pericolonic abscesses, sinus tracts, or peritonitis
   - Even without inflammation, diverticular disease is associated with exaggerated peristaltic contractions causing cramping and intermittent constipation and diarrhea
   - Rx: High fiber intake
II. IDIOPATHIC INFLAMMATORY BOWEL DISEASE (IBD)

Crohn's disease and ulcerative colitis are IDIOPATHIC, CHRONIC ULCERATING INFLAMMATORY diseases that can only be diagnosed when all specific causes of chronic enterocolitis have been ruled out. Both are diseases that occur primarily in young adults and increase the risk of carcinoma (ulcerative colitis more than Crohn's disease). Both are characterized clinically by periodic exacerbations and remissions. Treatment is based on anti-inflammatory drugs to control "activity" of disease and surveillance for dysplastic (and/or neoplastic) changes in the mucosa. High grade dysplasias, carcinomas and other complications of IBD require surgical resection. Both forms of IBD may have extraintestinal inflammatory manifestations involving the eye, joints, liver and biliary tree (e.g., primary sclerosing cholangitis).

A. CROHN'S DISEASE (CD)

Distribution: Primarily targets the terminal ileum (65-75% of cases) with both small and large bowel (usually right colon) involvement in 30% of cases but may affect any part of the GI tract. In 20-30% of cases, only the colon is involved.

Pathological features:
- Focal, patchy (as opposed to diffuse, confluent) distribution with normal "skip" areas between involved foci.
- Ulcerations are characteristically deep and sharp (fissuring ulceration). Fissures may extend through the entire bowel wall causing perforation and peritonitis or extend through structures adjacent to the bowel such as the uterus, vagina, abdominal wall, bladder or another bowel loop to form fistulas.
- The depth of the inflammatory process commonly mural scarring and stricture formation.
- Microscopically, noncaseating granulomas are found in about half of cases.

B. ULCERATIVE COLITIS (UC)

Distribution: Targets the colon exclusively ("colon-only" disease)

Pathological features:
- Diffuse, confluent distribution without "skip" areas. Process always begins in the rectum and progresses retrograde.
- May remain localized to the rectum (ulcerative proctitis) or left colon or may involve the entire large bowel (pancolitis).
- "Backwash ileitis" present in some cases of pancolitis.
- Inflammatory process is typically limited to the mucosa. Ulcerations are characteristically broad and shallow.
- Acute severe flare-up can lead to bowel paralytic dilation ("toxic megacolon").

Most important complication is malignant transformation:
- Risk is related to DURATION, EXTENT and SEVERITY of disease.
- Cancers may be multifocal, biologically aggressive and occur at a relatively young age (compared to non-IBD colon carcinoma).
- Surveillance colonoscopy with biopsies performed regularly (yearly or every two years) in patients who have had CUC for 7 years or more.
- High grade dysplasia or dysplasia (irrespective of grade) in the presence of a visible mass or lesion ("DALM") requires colectomy.
- Although colectomy is curative for colonic disease, it does not prevent the extraintestinal manifestations mentioned above.

SELECTED REFERENCES

1. Robbins and Cotran, Pathologic Basis of Disease, 6th ed., relevant sections in "Gastrointestinal Tract"