At a Harben Lecture in London in 1908, German scientist Paul Ehrlich described the ideal drug as a “magic bullet” (Zauberkegel). Such a drug would be aimed precisely at a disease site and would not affect healthy tissues. Today, over 3.5 billion prescriptions are dispensed each year in the United States to manage a broad number of health disorders. Although many drugs are aimed more accurately than their predecessors, none of them, as of yet, hit their targets exclusively. Several medications are associated with an increasing incidence of drug-induced (iatrogenic) adverse events, a frequent site of which is the GI tract. In fact, 10% of the drug-induced adverse effects are related to the GI tract. The consequences of such can range from asymptomatic histologic changes in the GI mucosa to fatal adverse events. In some instances, the adverse events are worse than the illness for which the drug was prescribed. However, many drug-induced adverse events are preventable. Therefore, it is becoming increasingly important to recognize both the clinical and pathologic manifestations of GI tract drug-induced injury early, so that the offending drug can be discontinued or replaced.

This review uses an organ-based approach to present both clinical information and pathologic findings to increase clinical awareness of the most common drug-induced GI conditions. Although each part of the GI tract has been considered separately, some drugs exert a common local effect (eg, esophagus), whereas others have more specific findings or principally a systemic mode of action. Because the number of drugs that are potentially toxic to the GI tract is almost countless, we focus on the most common and well-documented examples of drug-induced injury, in which endoscopic and/or histologic findings can be recognized.

**ESOPHAGUS**

**Pill esophagitis**

Pill esophagitis is the most common form of medication-induced esophageal injury and is related to both direct contact and facilitation of mechanisms that eventually lead to disruption of the mucosal lining. Damage to the underlying mucosa occurs because of a medication’s direct localized toxicity, generally caustic (acidic or alkaline) or hypopersmolar in nature. However, factors such as medication contact time, pill coating, and immediate versus sustained-release formulations likely all play a role. Altered anatomy (eg, stricture), motility disturbances, and ingestion parameters also may be contributing factors. Frequent areas of “hang-up” leading to prolonged mucosal contact include the level of the aortic arch, the level of an enlarged left atrium, and the gastroesophageal junction.

The most common presenting symptoms include severe retrosternal pain immediately after ingestion of food and liquid, frequently worse with inspiration, and odynophagia. A typical history usually can be obtained in which a patient took an offending medication immediately before bed, with just a small sip of water, or none at all. Symptoms can be severe but self-limited and generally resolve within a week. “Topical” agents such as sucralfate suspension or viscous lidocaine can provide temporary relief if dosed before meals. At times, narcotic medication may be necessary to alleviate pain. Rarely, parenteral hydration and/or nutrition are needed if pain is so severe that the patient cannot drink. Endoscopy is generally not necessary in the appropriate clinical setting, but if performed, typical findings include either a solitary ulcer or multiple ulcerations with localized exudate (Fig. 1A). Biopsies are generally not helpful, other than to exclude malignancy. Pathologically, the pattern of injury is consistent with a nonspecific esophagitis characterized by mucosal ulceration and...
Figure 1. Endoscopic and corresponding microscopic examples of esophageal and gastric drug-induced injury. A, The most common form of esophageal medication-induced injury is pill esophagitis. Although the endoscopic findings are nonspecific and characterized by mucosal ulceration with associated fibroinflammatory exudate, certain medications can demonstrate distinct microscopic findings. B, In the case of iron pill esophagitis, the iron pill imparts a dusky greyish discoloration within a background of granulation tissue (H&E, orig. mag. ×20). C, Sloughing esophagitis features prominent white plaques or membranes within the middle-to-distal esophagus. D, The typical histologic findings are a tone-toned appearance, with a superficial eosinophilic zone composed of pyknotic nuclei and an underlying normal-appearing basal zone (H&E, orig. mag. ×20). E, Sodium polystyrene sulfonate–induced injury to the gastric mucosa is characterized by erosion and/or ulceration (right lower corner) and F, rhomboid, basophilic crystals with a mosaic pattern (H&E, orig. mag. ×40). Another exchange resin that can mimic the effects of sodium polystyrene sulfonate is sevelamer carbonate. G, Sevelamer carbonate–induced esophageal injury is characterized by mucosal erythema, ulceration, and white exudates (figure kindly provided by Dr William Santangelo). H, Similar to those of sodium polystyrene sulfonate, sevelamer carbonate crystals are nonpolarizable with a broad, curved “fish scale” pattern, but of variable color (H&E, orig. mag. ×40).
associated fibroinflammatory exudate. Fortunately, bleeding from pill-induced ulceration is rare. In severe cases, long-term sequelae can lead to strictureing and rarely esophagorespiratory fistulization or perforation. Preventative treatment is best, educating patients to drink plenty of fluid and remain upright after taking a potentially offending medication.

The most common offending medications include nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, quinidine, potassium chloride, and bisphosphonates. NSAIDs may be the most common culprit, given the frequency of use by the general public. Tetracyclines and ferrous sulfate cause local acid burns given their acidic nature, whereas potassium chloride, clindamycin, and quinidine are caustic, but do not alter pH. It is believed that potassium chloride has local hyperosmolar toxicity because of its high salt concentration.9,10 Tetracyclines are the most common type of antibiotic to cause pill esophagitis, with doxycycline being the most frequent culprit.

Iron-induced injury is typically limited to the upper GI tract, and within the esophagus it can induce a chemical burn with erosive injury. Biopsies typically display luminal brown-black crystalline material adjacent to injured surface epithelium or admixed with luminal fibroinflammatory exudates (Fig. 1B). Confirmatory iron stains can be used to highlight iron deposition. Of note, sometimes exuberant proliferation of reactive fibroblasts and regenerative epithelial changes are seen near esophageal ulcers that contain iron crystalline. These changes can be so striking as to raise the suspicion of a malignant process.11,12 Bisphosphonate injury is caused by a caustic alkaline effect on the mucosa.13 The most common offender is alendronate, whereas cases secondary to etidronate and pamidronate have been described only as case reports. Risedronate appears to have minimal GI toxicity. Symptoms typically include retrosternal chest pain, dysphagia, and odynophagia. Endoscopically, a chemical esophagitis is seen, resembling severe reflux esophagitis. Frank ulceration and strictureing also can be present.13 The overall incidence of bisphosphonate-related esophageal toxicity has declined with better patient education, with specific instructions to take these agents with 8 ounces of liquid and remain upright for 30 minutes afterward.13 Additionally, the introduction of parenteral formulations has further decreased the use of oral bisphosphonates. Endoscopically, there tends to be more diffuse mucosal inflammation with exudate and pseudomembranes, resembling reflux esophagitis. On biopsy, histologic findings include ulcerative esophagitis with translucent but polarizable crystals and associated multinucleated giant cells.15

**Sloughing esophagitis**

Sloughing esophagitis is characterized by superficial necrotic squamous epithelium with both distinct endoscopic and histologic features.16,17 Patients are typically older, with a mean age > 50 years, and they present with a broad range of esophageal symptoms including dysphagia and/or globus sensation, odynophagia, noncardiac chest pain, heartburn, regurgitation, and cough. Nearly all patients have endoscopic disease involving the middle-to-distal esophagus with prominent white exudates or plaques (Fig. 1C). On biopsy, the abnormal esophageal squamous epithelium has a 2-toned appearance, with a superficial eosinophilic zone of necrosis and an underlying deeper squamous mucosa that is either normal or appears more basophilic because of basal cell hyperplasia (Fig. 1D). In between these two layers, there is a separate layer of neutrophils. In some cases, the superficial eosinophilic and necrotic epithelium is completely separated from the underlying deep basal epithelium.16 Although no specific cause for sloughing esophagitis has been identified, patients are more likely to be chronically debilitated and on multiple medications including central nervous system depressants.

**Chemotherapy agents**

Dactinomycin, bleomycin, cytarabine, daunorubicin, 5-fluorouracil, methotrexate, vincristine, and other chemotherapy regimens used in hematopoietic stem cell transplantation can all lead to oropharyngeal mucositis, with resultant odynophagia. This can involve the esophageal mucosa, but esophageal injury is more often seen in the absence of oral changes. Esophagitis is typically self-limited and resolves with cessation of the chemotherapy. Patients receiving chest radiation are at particularly high risk of “recall” esophagitis, which increases the severity of the esophagitis, resulting in lower doses of radiation being tolerated.7

Paclitaxel is an antineoplastic agent that interferes with tubulin and inhibits its polymerization into microtubules, which causes mitotic arrest. It can cause injury throughout the GI tract, but most commonly affects the esophagus. Histologically, the pattern of injury features epithelial necrosis and ulceration, in addition to ring-shaped, arrested mitotic spindles. Injury is thought to be dose related and resolves with cessation of the medication.18

**STOMACH**

**NSAIDs**

Although NSAIDs can affect any portion of the GI tract, resultant gastric pathology is most common. NSAIDs inhibit prostaglandin production, notably via the cyclooxygenase (COX) 1 pathway, which helps maintain mucosal health and integrity.4,17 Cytoprotective properties of prostaglandins include stimulation of mucin (glycoprotein) and bicarbonate secretion by epithelial cells, along with enhancement of mucosal blood flow and oxygen delivery to epithelial cells via vasodilatory effects. Through their systemic effect, NSAIDs inhibit production of prostaglandins, which can lead to gastric mucosal damage to include reactive
gastropathy, characterized by a constellation of findings: fo-veolar hyperplasia with mucin depletion, reactive nuclear hyperchromasia, lamina propria congestion, and smooth muscle proliferation. Additionally, frank ulcera-ctions caused by NSAIDs can range from super-mucosal erosions can be seen. The spectrum of peptic ul-ceration caused by NSAIDs can range from superficial and small to giant and deeply cratered. Acute hemorrhage is not uncommon.

Iron
Iron pill gastritis is a relatively common finding in pa-tients receiving iron supplementation. Endoscopically and microscopically, focal mucosal staining with brown or black pigment is seen frequently. Although erosive mucosal change can be seen, frank ulceration is less common. Bi-opsies may reveal crystalline iron adjacent to superficial epithelium, deposited in the lamina propria or admixed in inflammatory surface exudate. Iron can have a locally corro- sive effect, but it is unclear whether it causes a direct pathologic injury or is just staining an underlying mucosal lesion. If pathologic, gastric disease is generally related to the amount of iron deposition within the epithelium, lam-ina propria, and mucosal glands.

Resins
Sodium polystyrene sulfonate is a cation-exchange resin for the management of hyperkalemia. It can be instilled into the lower GI tract as an enema preparation or into the upper GI tract, either orally or by nasogastric tube. When administered to the upper GI tract, sodium ions are released from the resin and exchanged for hydrogen ions in the stomach. As the resin passes through the intestines, hydrogen is exchanged for potassium, which is elim-inated in the feces along with the remainder of the resin, thereby lowering serum potassium levels.

Previously, sodium polystyrene sulfonate was adminis-tered as a suspension in water. Although that method is well-tolerated, some patients developed gastric and bowel opacifications as a result of crystalline resin concretions. Sodium polystyrene sulfonate was subsequently given as a suspension in hypertonic sorbitol, reducing the fre- quency of bezoar formation and colon impaction by pro-motion of osmotic diarrhea. However, studies have shown that the sorbitol component can lead to colon necrosis and that uremic patients are most susceptible to the vascular shunting induced by the osmotic load.

More recently, it has become apparent that sorbitol can lead to erosive and ulcerative injury of the upper GI tract in patients taking oral preparations. Importantly, these upper GI tract lesions seem to be reversible and are typically not associated with serious sequelae. In most instances, sodium polystyrene sulfonate is easy to recognize in histologic biopsies, with the identification of rhomboid or triangular, nonpolarizable, basophilic crystals, which show a characteristic mosaic pattern. These crystals typically are found adherent to the surface epithelium or within sloughed, inflammatory exudates.

Another resin encountered in medication-associated up-per GI tract injury is cholestyramine. Cholestyramine is used to treat hypercholesterolemia and is a bile acid-binding resin that sequesters bile in the GI tract to prevent reabsorp-tion. It is a strong ion resin that can exchange its chloride ions with bile acids, forming insoluble complexes that are excreted in the feces. When bile acids are excreted, plasma cholesterol is converted to bile acid to normalize bile acid levels, effectively lowering plasma cholesterol concentra-tions. The gastric endoscopic findings of cholestyramine-induced injury are nonspecific and can range from superficial erosions to deeper ulcerations. Histologically, the crystalline structure of cholestyramine is similar to that of sodium polystyrene sulfonate; however, the former has greater opacity, lacks a mosaic pattern, and is usually red in color on hematoxylin-and-eosin stained slides. Importantly, the effects of both sodium polystyrene sulfonate and cholestyramine seem to be reversible and are typically not associated with serious sequelae.

More recently, GI tract mucosal injury has been recog-nized with the anion exchange resin, sevelamer carbonate. Sevelamer carbonate acts as a phosphate binder and is used for the treatment of hyperphosphatemia in patients with chronic renal disease. These agents contain multiple amines separated within a carbon polymer backbone. The amines exist in a protonated form within the intestines and interact with phosphate molecules through ionic and hydrogen bonding. By binding phosphate within the GI tract and decreasing absorption, sevelamer carbonate lowers the phosphate concentration within the serum. Chronic mucosal injury has been reported to occur throughout the GI tract, resulting in ulceration and super-fi-cial necrosis. Histologically, sevelamer carbonate consists of nonpolarizable crystals with broad, curved “fish scales” and variable color.

Chemotherapy agents
Chemotherapeutic agents can affect any region of the GI tract. In the stomach and duodenum, ulcers with nu-clear irregularity have been associated with hepatic artery infusion chemotherapy and selective internal radiation. From an endoscopic perspective, ulcerations can mimic gastric carcinoma, and the histologic features are necessary to differentiate these effects from neoplasia. For both ther-apies, a prominent finding is the presence of striking nuclear atypia, where numerous enlarged, bizarre nuclei, often with vesicular chromatin and large, irregular nucleoli are seen. Features indicative of chemotherapy-related gastric ulcers are architectural preservation, nuclear atypia confined mainly to deeper glands, preservation of nuclearto-cytoplasmic ratio, cytoplasmic vacuolization, paucity of mitotic figures, and the presence of similar nuclear changes within granulation tissue stromal cells. By contrast, uniform
anaplasia within surface foveolar epithelium, with a high nuclear-to-cytoplasmic ratio and frequent mitoses suggests true carcinoma and/or dysplasia. Further, the presence of small, black microspheres within mucosal capillaries is nearly diagnostic of selective internal radiation therapy–induced injury.6,25

Colchicine
In addition to hepatic artery infusion chemotherapy and selective internal radiation, microtubulin inhibitors can similarly damage the gastric antrum and duodenum. Colchicine, which is used for the treatment of gout, costochondritis, and pericarditis, mainly results in endoscopic mucosal erosions in the setting of renal insufficiency. Biopsies demonstrate distinctive ringed mitoses as seen in paclitaxel-induced esophageal injury, epithelial pseudotractivation, loss of nuclear polarity, and abundant crypt apoptotic bodies.26

SMALL AND LARGE INTESTINES

NSAIDs
Within the small intestine, the pathology of NSAID-induced injury is most commonly seen in the duodenum and distal ileum.27 Duodenal injury is similar to that seen within the stomach, notably duodenitis, erosions, and/or ulcers most commonly located in the duodenal bulb. Unfortunately, the histologic features of NSAID-associated ulcers are nonspecific, although they usually are not associated with abundant chronic inflammation. Another adverse event of NSADS is “diaphragm disease.” It consists of multiple, web-like luminal protrusions of fibrotic mucosa that narrow the lumen.28 Initially, diaphragm disease was considered more common in the distal ileum; however, recent studies incorporating wireless capsule endoscopy suggest a more equal distribution throughout the small bowel. Although diaphragm disease is considered a gross diagnosis, histologic correlates describe columns of fibrosis, often eroded at its tip, extending from the mucosa into the deeper regions of the submucosa, with variable amounts of smooth muscle, ganglion cells, and vessels.29,30 Overt bleeding from diaphragm disease is rare, but a presentation of iron deficiency anemia caused by chronic blood loss is not uncommon.

Colon injury caused by NSAID use typically affects the right side of the colon. Similar to the pathology in the small intestines, erythema and ulceration can be seen and show nonspecific histologic findings on biopsy. NSAID-induced colon injury is directly related to prostaglandin inhibition. In fact, in the setting of chronic colitis, COX2 is activated and results in prostaglandin synthesis that contributes to ulcer healing and disease stability in patients with inflammatory bowel disease. For this reason, it is recommended that NSAIDs be avoided in all patients with inflammatory bowel disease. However, the pathophysiology of colon injury is not completely understood, because COX2 inhibitors also exacerbate quiescent disease.31

Olmesartan
Olmesartan medoxomil is an angiotensin II receptor blocker used to treat high blood pressure. The drug works by inhibiting the effects of angiotensin II, a potent vasoconstrictor and one of the key contributors to cardiovascular and renal disease. The safety and tolerability of olmesartan has been evaluated in several clinical trials for 6 to 12 weeks. Overall, patients tolerated the drug well, and the incidence of adverse events was similar to that of placebo (42.2% and 42.7%, respectively).32-34 Recently, olmesartan has been linked to severe GI issues in patients taking the drug for several months to years.35 The symptoms, which include nausea, vomiting, diarrhea, weight loss, and electrolyte abnormalities, are reminiscent of those in patients with celiac disease. In fact, the endoscopic and microscopic findings within the duodenum are indistinguishable and characterized by partial-to-total villous atrophy, lymphoplasmacytic expansion of the lamina propria, and prominent intraepithelial lymphocytosis (Fig. 2A and B). However, celiac disease serology results (IgA anti-tissue transglutaminase and IgA anti-endomysial antibody testing) are negative, and patients are unresponsive to a gluten-free diet. Cessation of the medication results in both clinical and histologic improvement.

Mycophenolate mofetil
Mycophenolate mofetil (MMF) is an immunosuppressant agent approved for solid organ transplantation in 1995, used to prevent allograft rejection.36 It is a prodrug of mycophenolic acid which is an antibiotic substance derived from Penicillium stoloniferum. It exerts its effect by inhibiting inosine monophosphate dehydrogenase, an enzyme in purine synthesis. It prevents T-cell and B-cell proliferation as well as inhibiting leukocyte recruitment to inflammatory sites. Reported side effects of MMF include diarrhea, nausea, vomiting, abdominal pain, malabsorption, and bleeding. Symptoms are more likely to occur if MMF therapy is started later after transplantation or if the patient has an elevated creatinine level. MMF-induced injury can affect the entire GI tract, with endoscopic evidence of ulcers and erosions. The degree of inflammation can span mucosal erythema, congestion, aphthous ulcers, and confluent ulceration (Fig. 2C). This occurs with severity ranging from mild to life threatening and is associated with both short-term and long-term exposure. Treatment typically consists of dose reduction or complete cessation.37 A change to mycophenolic acid, a delayed-release MMF formulation with a lower GI side-effect profile, may be beneficial for patients with mild symptoms. Histologically, the pattern of injury is typified by prominent crypt apoptosis as seen in graft-versus-host disease and infectious etiologies (Fig. 2D).38,39 In addition, there are often dilated crypts with eosinophils and neutrophils.40

In severe cases, there may be crypt dropout, with only small nests of residual endocrine cells in the lamina propria. Over time, crypt distortion may develop, mimicking chronic inflammatory disease. Thus, the differential diagnosis can be broad and includes graft-versus-host disease, inflammatory bowel disease, ischemia, and acute self-limiting enterocolitis.

Monoclonal antibodies

Ipilimumab is a humanized monoclonal antibody developed to reduce and overcome cytotoxic T-lymphocyte antigen 4. Its mechanism of action is a negative feedback regulator of T-cell antitumor response. It is used as an adjuvant to experimental tumor immunization protocols in the treatment of a growing number of malignant neoplasms including malignant melanoma, ovarian cancer, renal cell carcinoma, and prostate cancer. Adverse events are seen in up to 40% of patients and consist of dermatitis, endocrinopathies, uveitis, nephritis, hepatitis, and diarrhea. More recently, GI tract involvement has been reported, most commonly affecting the colon. Patient presentation ranges from mild with abdominal cramping and diarrhea to severe, ultimately resulting in fatal colitis. Colon toxicity is seen in approximately 20% of patients, typically occurring within a short period of time after administration. Fatal colitis has been reported in up to 5% of cases, and life-threatening colon perforation was reported in 4 of 700 cases. Should enterocolitis develop, treatment is generally supportive. In severe cases, intravenous steroids have been given, and if no improvement, resection with a diverting ileostomy has been required. The endoscopic appearance can vary from normal to diffusely erythematous and ulcerated mucosa (Fig. 3A). In some cases, this condition can be difficult to differentiate grossly from inflammatory bowel disease. The histologic findings include a lymphoplasmacytic expansion of the lamina propria, with an increase in intraepithelial lymphocytes, prominent apoptosis, and elongation of the crypts (Fig. 3B). Cryptitis and glandular inflammation are noted within the colon as well as the stomach and ileum. In some cases, villous blunting occurs within the duodenum and ileum. Tremelimumab is another cytotoxic T-lymphocyte antigen 4 monoclonal antibody used in the treatment of malignant melanoma and has shown an adverse event profile similar to that of ipilimumab.

Several other biologic agents have been shown to cause colon abnormalities. Rituximab is an anti-CD20 monoclonal antibody used in the treatment of rheumatologic conditions such as rheumatoid arthritis and lupus. This antibody targets B cells and, within the GI tract, depletes the intestinal B-cell population. Although the findings are largely published as case reports, multiple adverse events have been reported and implicate rituximab in the development of ulcerative colitis and exacerbation of underlying colitides in otherwise healthy individuals.

Bevacizumab is another humanized monoclonal antibody against vascular endothelial growth factor receptor...
and is used in the treatment of metastatic colon cancer and lung cancer. Its effects are thought to be related to inhibition of tumor neovascularity. This drug has, however, been associated with bowel perforations and a propensity for anastomotic leakage in patients who have undergone previous colon resection.

Chemotherapy agents

As previously mentioned, chemotherapy agents can cause injury to any part of the GI tract through systemic effects on immunity and the ability to fight off infections. They can lead to cytopenias, specifically neutropenia. Neutropenic enterocolitis, better known as “typhlitis,” can occur and consists of hemorrhagic necrotizing inflammation and ulceration within the terminal ileum and cecum. Overlying bacterial and fungal overgrowth is common, which can lead to sepsis. It is most common in leukemic patients, associated with use of cytosine arabinoside, cisplatin, vincristine, doxorubicin, 5-fluorouracil, and mercaptopurine. Treatment consists of antibiotics, filgrastim to improve neutropenia, and chemotherapy dose reduction.

Corticosteroids

Steroid use can cause both upper and lower GI tract injury. Within the upper GI tract, steroid use predisposes to erosions and ulceration. Within the colon, corticosteroid use has been linked to both intestinal malakoplakia and sigmoid colon diverticular perforation. Although more commonly found within the genitourinary tract, malakoplakia is a rare inflammatory condition that appears
endoscopically as a yellowish papule, plaque, or ulceration. It reflects a curious response to phagolysosomal digestion of enteric bacteria and microscopically consists of a histiocytic infiltrate of epithelioid cells with eosinophilic granular cytoplasm (von Hansemann cells) and the presence of intracellular and/or extracellular basophilic, laminated calcifications with a targetoid appearance (Michaelis-Gutmann bodies). Sigmoid diverticular perforation is a rare adverse event in patients receiving corticosteroids; however, the risk increases in patients with rheumatoid arthritis.

**Diuretics**

Ischemic injury to the GI tract is categorized by an intermittent decreased blood flow and/or lack of oxygen that leads to necrosis and is caused by a multitude of factors including certain drugs. Classic symptoms consist of crampy abdominal pain and hematochezia. The disease is often but not always self-limited, with treatment consisting of supportive measures and removal of the offending agent. Elderly individuals with underlying cardiac and vascular disease are the most susceptible, and within this category a significant proportion are on diuretics. Diuretics exert their effect through volume depletion and cause an overall state of decreased blood flow that can lead to nonocclusive ischemia. Injury most often involves the colon, followed by the small bowel and rarely the esophagus and stomach.

Endoscopically, geographic areas of ulceration and possibly pseudomembrane formation are seen (Fig. 3C). This can be accompanied by marked submucosal edema, which in some cases may mimic a mass lesion. The watershed areas around the splenic flexure of the colon are the most common sites for ischemic colitis. Chronic or healed ischemic lesions may form isolated strictures that resemble those of Crohn’s disease. Histologically, ischemic lesions show superficial mucosal necrosis with sparing of the crypt base, giving the crypts a withered appearance. Hemorrhage and hyalinization of the lamina propria also is seen (Fig. 3D).

**Sodium polystyrene sulfonate**

The effects of sodium polystyrene sulfonate within the stomach were discussed earlier, and its histopathologic findings in the lower GI tract are analogous. Injury also can be connected to sorbitol, which results in rapid electrolyte shifts that are seen frequently in uremic patients. Thus, it is no longer recommended in this patient population. Within the colon, the endoscopic manifestations often are severe and include massive dilatation, pseudomembrane formation, and ulceration. This can ultimately result in transmural necrosis and colon infarction. Up to 30% of patients with sodium polystyrene sulfonate-associated injury are reported to require surgical resection. These patients are typically those that received enema preparations in comparison to oral formulations in which GI tract injury is less prominent.

**Oral contraceptives and hormone replacement therapy**

Ischemic colitis is traditionally associated with elderly patients who have comorbid conditions. In young patients with no obvious predisposing factors, ischemic colitis can be seen in those taking certain medications including estrogens. Estrogen is a common drug in postmenopausal women, and it is a mainstay ingredient in oral contraceptive pills. Estrogen produces a hypercoagulable state and can lead to mesenteric vein thrombosis, which was identified in the majority of reported young women who developed ischemic colitis. The endoscopic and histologic appearance is similar to that in other causes of ischemic colitis, with ulceration and transmural necrosis that affects not only the splenic flexure but frequently the rectum as well.

**Ergotamine**

Ergotamine is another drug used in both younger and older populations as a modality to induce remission of migraine headaches. Its mechanism of action is to induce a localized ischemia caused by vasospasm, which can lead to a form of ischemic colitis within the colon, typically consisting of multiple, shallow rectal ulcers. This is typically self-limited and not consistent with a diffuse area of ischemia seen in other forms of ischemic colitis. Furthermore, the watershed area is not affected, likely because of localized ischemia. Histologically, biopsies reveal mucosal ulceration consistent with the endoscopic appearance, and cessation of the drug leads to reversal of pathology.

**Glutaraldehyde**

Glutaraldehyde was a common agent used to disinfect colonoscopes. It is used rarely today because it has been identified as a contact irritant that leads to proctitis and/or colitis within hours of procedures. Fortunately, the inflammation and irritation are self-limited, and patients typically recover quickly after the procedure.

**Bowel preparation**

Bowel preparation for sigmoidoscopy and colonoscopy may induce a number of mucosal injuries. The most common bowel preparations consist of balanced electrolyte solutions containing polyethylene glycol. Previously, oral sodium phosphate preparations also were commonly used. Oral sodium phosphate preparations consist of both monobasic and dibasic sodium phosphates that work as an osmotic laxative by drawing fluids into the GI tract. Acute phosphate nephropathy has been reported with the use of oral sodium phosphate preparations for bowel cleansing. Given this, the U.S. Food and Drug Administration has required that a boxed warning be added to the label of Visicol (Pharmaceutical Manufacturing Research Services Inc, Horsham, Pa) and Osmoprep (Salix Pharmaceuticals Inc, Raleigh, NC), which are available by prescription only. Fleets Phosphosoda (C.B. Fleet Co, Lynchburg, Va) is available over the counter.
for use as a laxative; however, it is no longer recommended for bowel cleansing before procedures, given the risk of acute nephrotoxicity. The most common endoscopic lesion seen with the use of oral sodium phosphate preparations is the presence of aphthous-like lesions—small foci of pale mucosa surrounded by erythematous rings that look like shallow erosions. These aphthous-like lesions have been described in up to 25% of patients after sodium phosphate bowel preparations. Histologically, they are usually large lymphoid aggregates. These lesions disappear on repeat colonoscopy by using alternate bowel preparations and therefore, are clinically irrelevant. In a small subset of patients, oral sodium phosphate is believed to induce small foci of neutrophilic cryptitis, with scattered apoptotic bodies at the crypt base (focal active colitis), which could mimic true GI disease.

**Anthranoid laxatives**

Anthranoids are widely used herbal laxatives to treat acute and chronic constipation. The leaves and pods of the Senna genus of flowering plants are the most common source of anthranoids. The laxative effect is hypothesized to be caused by two independent mechanisms: increased colon motility and alterations in colon absorption and secretion, resulting in fluid accumulation. The motility changes are caused by anthranoid-induced epithelial cell apoptosis. The disruption of the mucosal integrity triggers histamine, serotonin, and prostaglandin release that results in increased large intestinal transit. In addition, anthranoids uncouple mitochondrial oxidative phosphorylation, resulting in decreased adenosine triphosphate production. Lower intracellular adenosine triphosphate levels, combined with direct interaction of the Na+/K+ adenosine triphosphatase system on the basolateral membrane of the enterocyte, leads to breakdown of the ion gradient over the epithelial cell membrane. This prevents absorption of sodium and water from the bowel lumen.

Chronic anthranoid laxative use often is associated with pseudomelanosis coli. In fact, a reported 73.4% of patients using anthranoid laxatives chronically develop pseudomelanosis coli. It generally evolves after 4 to 12 months of laxative intake and disappears 6 to 11 months after withdrawal.

Pseudomelanosis coli is a brownish pigmentation of the colon (Fig. 3E) and is caused by the accumulation of dark brown pigment in macrophages of the lamina propria (Fig. 3F). It may affect the entire length of the colon, including the appendix, and rarely involves the small intestine. Originally, the pigment was considered to be melanin or a melanin-like substance, and, therefore, the name melanosis coli was introduced. This was later changed to pseudomelanosis coli as the pigment proved to be more characteristic, both histochemically and ultrastructurally, as lipofuscin. Lipofuscin accumulates by phagocytosis of apoptotic epithelial cells. Although there is a strong association with anthranoid laxatives, many patients with pseudomelanosis coli do not report a history of laxative use. Some may be ingesting them inadvertently; for example, ingestion of aloe vera, which contains anthranoids, as a “wellness drink.” In addition, pseudomelanosis may result from any process associated with epithelial apoptosis, such as NSAIDs use, and it has been described in patients with inflammatory bowel disease.

**Summary**

Medications play an integral role in the health and well-being of patients. However, a large number of medications are reported to damage one or more segments of the GI tract, either directly or indirectly, resulting in a variety of clinicopathologic findings. Although some findings are pathognomonic for specific drugs, many more demonstrate nonspecific pathology. Early recognition of GI tract drug-induced injury is critical because the consequences of prolonged use, in some instances, can be fatal. Reducing the incidence of adverse effects requires an appropriate index of suspicion and good communication between the gastroenterologist and pathologist, both of which can significantly impact patient care.

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patients as a result of sodium polystyrene sulfonate (Kayexalate) in 
36. Parfitt JR, Jayakumar S, Driman DK. Mycophenolate mofetil-related 
gastrointestinal mucosal injury: variable injury patterns, including graft-
changes in colonic biopsies in patients treated with mycophenolate 


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1. NSAD-associated GI injury includes
   a. Pill esophagitis
   b. Upper esophageal webs
   c. Diaphragm disease of the small bowel, often associated with iron deficiency
   d. Rectal ulcerations and structuring

2. Match the drug with the typical GI injury:

   A. NSAIDs  1. Diffuse distal esophagitis
   B. bisphosphonates  2. Small bowel diaphragm disease
   C. kayexalate  3. Severe colitis and colon perforation
   D. Iplilumab  4. Colon necrosis
   E. Doxycycline  5. Mid esophageal ulcer
   F. Estrogens  6. Ischemic colitis

3. True or False

   3. Beyond the stomach, NSAID injury is most common in the duodenum and distal ileum
   4. Pseudomelanosis coli from anthranoid laxative use is permanent, even after stopping laxative use
   5. Kayexalate enema colon injury is due to osmolar injury, biopsies may be diagnostic
   6. Olmesartan can cause a celiac sprue-like illness with typical small bowel microscopic changes and positive TTG-IgA antibodies
   7. Mycophenolate mofetil can cause GI tract ulcers and erosions and with chronic use may lead to microscopic changes typical of chronic colitis
   8. Chemotherapy associated esophageal injury is almost always associated with oral mucositis
   9. Esophageal biopsies typically show pathognomonic evidence of pill esophagitis
   10. Melanin is the pigment responsible for the discoloration of the colonic mucosa in patients taking anthranoid laxatives
   11. Iron-induced GI injury is most common in the distal small bowel
   12. Malakoplakia of the colon may be an adverse event of chronic corticosteroid use
   13. Iron-induced esophageal or gastric injury may have diagnostic findings on mucosal biopsy