Fifth Edition

First Principles of Gastroenterology

The Basis of Disease and an Approach to Management

JANSSEN-ORTHO

A.B.R. Thomson and E.A. Shaffer, editors

5
The Stomach and Duodenum

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1. INTRODUCTION

Diseases of the GI tract are common, accounting for one out of seven complaints, and disorders of the stomach and duodenum make up a large part of these.

It has been known for many centuries that the gastric juice is acidic in nature, but it was not until 1824 that William Prout established that the acid in the stomach is hydrochloric acid. Since then physicians have been fascinated by the ability of the healthy stomach and duodenum to withstand hydrochloric acid and pepsin. In particular, the mechanisms controlling gastric secretion have been extensively studied in the hope of finding a satisfactory way to explain and treat peptic ulcer disease. Further studies turned to the role of mucus, bicarbonate and prostaglandins in the maintenance and defence of the gastric mucosa against acid injury. In 1983 Marshall and Warren isolated the bacteria now known as Helicobacter pylori (Figure 1) from gastric biopsies in duodenal ulcer patients and a new era in the understanding and treatment of gastroduodenal disease was born. This chapter will review the anatomy, physiology and related common disorders of the stomach and duodenum.

2. ANATOMY

2.1 General Anatomy

The stomach is the most capacious part of the GI tract and lies between the distal esophagus and the duodenum. It is situated entirely within the abdomen below the diaphragm (Figure 2). The body of the stomach lies

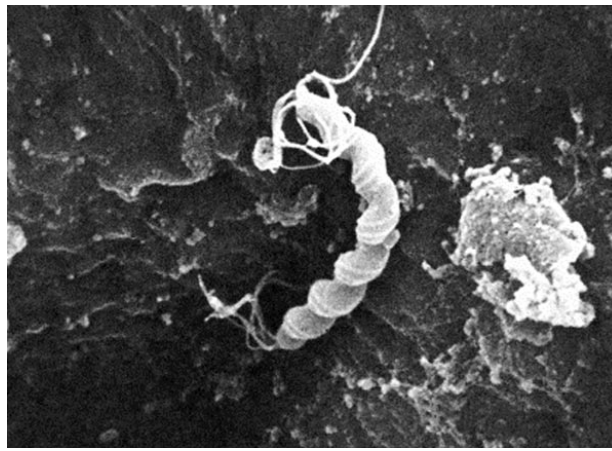

FIGURE 1. Helicobacter pylori. (Courtesy of McMaster University Medical Centre Electron Microscopy Lab.)

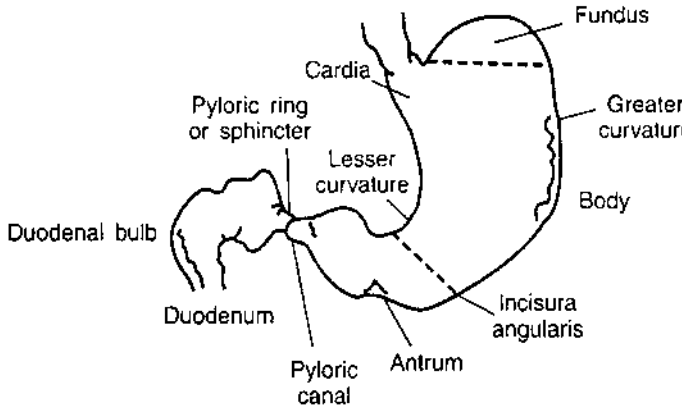

FIGURE 2. Anatomic divisions of the stomach.

slightly to the left of the midline; the antrum crosses the spinal vertebrae at the level of T10-L1, and the pylorus lies to the right of the vertebral column. The duodenum is predominately retroperitoneal and comprises the cap, the descending and the distal portions.

The greater curvature is some three or four times the length of the lesser curvature. A point known as the angulus or incisura may be defined on the

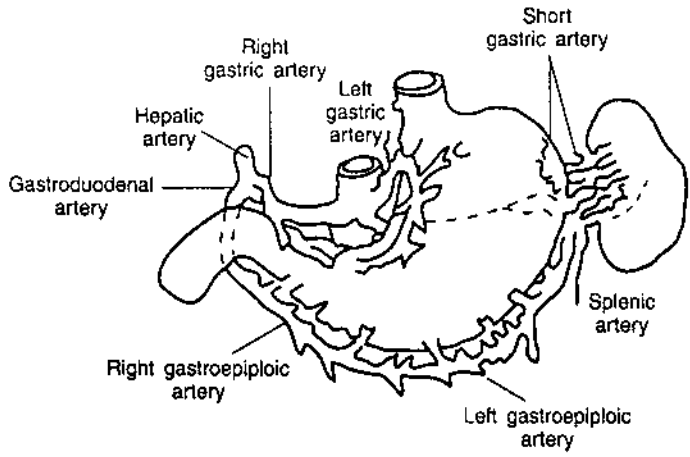

FIGURE 3. Blood supply to the stomach.

lesser curvature. This point is relatively constant and marks a change from the prominent rugal folds of the gastric body to the smoother, less-prominent folds of the antrum.

The stomach and duodenum lie in close proximity to a number of important anatomic structures. Anterosuperiorly are the left diaphragm and left lobe of the liver, while the body and tail of the pancreas lie posteriorly. Laterally to the left are: the hilum of the left kidney, the left adrenal gland and, above that, the spleen. These organs form the stomach bed and are separated from it by the lesser omentum and the lesser sac. The duodenum, apart from the cap, lies retroperitoneally. The second and distal parts surround the head of the pancreas, while the cap, which is attached to the lesser omentum, lies anterior to the head of the pancreas.

2.2 Blood Supply

The main arterial blood supply (Figure 3) arises from the celiac axis. The common hepatic artery gives rise to the gastroduodenal artery and the right gastric artery, which then anastomoses with the left gastric artery. The splenic artery gives rise to the short gastric arteries that supply the body along the greater curvature of the stomach. The right and left gastroepiploic arteries also form an anastomosis along the greater curvature.

Venous drainage essentially follows the arterial supply but passes to the portal venous system and its tributaries, the splenic vein and the superior mesenteric vein. Veins from the fundus communicate with veins draining the

lower third of the esophagus and form a connection between the systemic and portal venous systems. This connection assumes clinical importance if portal venous pressure rises when venous flow is reversed through the esophageal veins leading to esophageal or gastric fundal varices.

Lymphatic drainage is via the pancreaticosplenic nodes, the left gastric nodes and the pyloric nodes, and then via the celiac group to the preaortic lymph nodes and the cisterna chyli.

2.3 Nerve Supply

The nerve supply is both sympathetic and parasympathetic. The vagal supply arises via the anterior and posterior trunks, which pass through the diaphragm on either side of the esophagus before giving rise to the hepatic and celiac branches. The hepatic branch supplies further branches to the anterior surface of the body of the stomach and to the pyloric region, while the celiac branch passes to the celiac plexus and the posterior aspect of the body of the stomach. The vagal fibres anastomose with ganglion cells of the stomach with the muscle layers, forming Auerbach's plexus or, in the submucosa, forming Meissner's plexus.

The sympathetic nerve supply arises from the spinal cord between T6 and T10 and passes to the sympathetic ganglia. The parasympathetic supply contracts the stomach, relaxes the pylorus and stimulates acid, pepsin and mucus secretion, whereas sympathetic stimulation constricts the blood supply and reduces gastric motor activity and secretion while the pylorus is contracted.

2.4 Structure of the Stomach and Duodenum

The stomach and duodenum are comprised of an outer serosal coat, a muscular layer, submucosa and mucus membrane. The rugal folds ridge the mucosal surface and are created by contractions of the muscularis mucosa. They are especially prominent in the body of the stomach and are less obvious in the antrum. The glands of the stomach are of two main types – gastric and pyloric – both of which are closely packed in the columnar epithelium. The gastric glands (known as oxyntic glands) make up 70–80% of the total and are responsible for secreting mucus, pepsinogen, hydrochloric acid and intrinsic factor (Figure 4). The pyloric glands, which secrete mucus and gastrin, make up only about 15% of the total. A line of demarcation can usually be seen between the gastric and pyloric glands in the region of the incisura.

The gastric glands differ in cell type: the chief or peptic cells secrete pepsinogen, while the parietal or oxyntic cells secrete hydrochloric acid and intrinsic factor. The endocrine cells of the antrum secrete gastrin and 5-hydroxytryptamine. In the duodenum, the first 4–5 cm of mucosa are smooth, but in the descending duodenum, the mucosa is thrown into crescentic

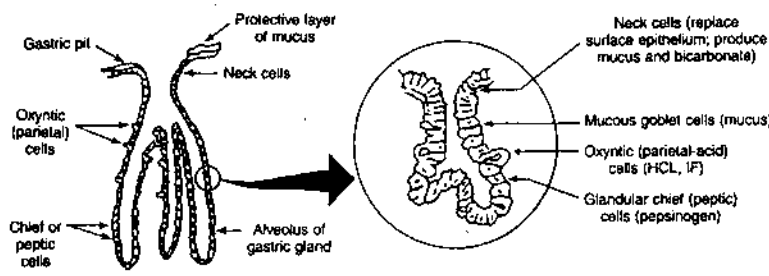

FIGURE 4. Microscopic appearances of gastric pit and glands.

folds. The mucosa is lined with columnar, goblet, Paneth's and endocrine cells. The columnar cells line the villi and crypts, which increase in size in the second and third parts of the duodenum. Brunner's glands, which are similar to pyloric glands, are a characteristic feature in the duodenal submucosa.

3. GASTRIC PHYSIOLOGY

3.1 Gastric Motility

The stomach's primary function is to store and mix its contents. Foods enter the stomach with synchronized relaxation of both the upper and lower esophageal sphincters. Cardia and fundic regions also relax during this process and this is manifested in the ability of the stomach to enlarge to accommodate a full meal without a change in muscle tension. The corpus of the stomach serves as a food reservoir while the antrum mixes, homogenizes and propels digested food to the duodenum via contractions of longitudinal, circular and oblique gastric muscle layers. This peristaltic movement originates in the region of incisura angularis and spreads to the antrum toward the pylorus. Emptying takes place at the pyloric sphincter as it opens during the resting phase, incompletely and intermittently allowing small portions of liquid to pass, while most of the material is forced back into the corpus for further homogenization.

Factors that influence gastric motility can be classified as myogenic, neural and chemical. Gastric pacemakers control the frequency and direction of muscle contractions. Gastric distension caused by solid or liquid food stimulates both intrinsic nerves and vagal afferents, resulting in peristaltic contractions and increased gastric emptying. Gastrin increases the force of contraction while delaying the emptying. The emptying is influenced by physico-chemical properties of processed food. Liquids empty

more rapidly than solids whereas triglycerides, fatty acids and HCL slow down emptying. The rate of emptying is related to the square root of the volume, resulting in a constant proportion of propelled food per time unit.

3.2 Gastric Secretion

The thick layers of gastric mucosa secrete gastric juice, which contains two key substances involved in digestion: hydrochloric acid and pepsin. Gastric juice also contains mucus, bicarbonate, water, and minerals – all involved in protecting the gastric mucosa from the destructive forces of acid and pepsin and also intrinsic factor, required for the absorption of vitamin B_{12}.

3.2.1 ACID SECRETION

Gastric glands of the oxyntic mucosa in the corpus of the stomach secrete acid. Highly specialized parietal cells, rich in mitochondria and equipped with cellular membrane-bound enzyme H^+/K^+ ATPase, have the ability to secrete protons against their extracellular gradient. As a result, a high concentration of hydrogen ions is generated in canaliculi at the apical membrane of parietal cells, which diffuse to the lumen of oxyntic glands and are subsequently propelled to the lumen of the stomach, reaching concentrations as high as 0.16 M. This complex biochemical process is activated and regulated by three major pathways: neural, paracrine and hormonal.

Post-ganglionic neurons that originate in the vagus terminate in the myenteric and the submucosal plexus in the proximity of parietal cells. Other auxiliary cells, including the histamine-producing enterochromaffin-like (ECL) cells, gastrin-producing G cells, and somatostatin-producing D cells, secrete without formation of synaptic junctions. Acetylcholine from these nerve endings directly diffuses toward parietal cells and binds directly to M3 receptors, causing an influx of Ca^{2+} ions and activating acid secretion. Furthermore, parietal cell activation occurs in an indirect manner by neural stimulation of the ECL cells. Neurally stimulated G and D cells also regulate the release of histamine from ECL cells. In addition, a number of neuropeptides released from nerves in the gastric mucosa, such as gastrin-releasing peptide (GRP), calcitonin gene related peptide (CGRP), galanin, and PACAP, express a modulatory effect on acid secretion. In total, about 40% of acid secretion can be attributed to the neural pathway.

Paracrine regulation of acid secretion is restricted to two pathways: release of histamine from the aforementioned ECL cells, and release of somatostatin from D cells. These two pathways are antagonistic in nature, as histamine stimulates acid secretion via specific H2 receptors, resulting in the increased synthesis of cAMP and subsequent acid production, while somatostatin interacts with parietal cells via the SS2 receptor, expressing potent antisecretory properties.

TABLE 1. Causes of hypergastrinemia

With acid hypersecretion
Gastrinoma
Isolated retained gastric antrum
Antral G-cell hyperplasia
Massive small bowel resection
Pyloric outlet obstruction
Hyperparathyroidism
With variable acid secretion
Hyperthyroidism
Chronic renal failure
Pheochromocytoma
With acid hyposecretion
Atrophic gastritis
Pernicious anemia
Gastric cancer
Postvagotomy and pyloroplasty

A variety of gastrointestinal hormones are secreted into the gastric capillaries, including: cholecystokinin (CCK), peptide YY, enterogastrone, and secretin, but it is gastrin that remains the major regulator of acid secretion. Although parietal cells possess the receptors for gastrin, its major stimulatory mechanism of action is attributed to the release of histamine from ECL cells. Gastrin production is regulated primarily by the negative feedback mechanism; acidification of the gastric lumen inhibits gastrin production. This pathway is a major component of meal-stimulated acid secretion. An abnormality in this pathway may lead to hypergastrinemia (Table 1).

Among alternative pathways, the production of prostaglandins by cyclooxygenases, mainly PGE2, remains a critical factor in gastric homeostasis. Prostaglandin E2 inhibits acid secretion through the EP3 receptor and the fluctuation of its levels as a result of NSAID therapy remains a major concern in preserving the integrity of the gastric mucosa.

3.2.2 PEPSINOGEN SECRETION

Pepsinogen, a precursor to pepsin, is produced by chief cells located near the base of the gastric glands throughout the stomach and the duodenum. There are two major forms, pepsinogen A and pepsinogen B, each with different molecular structure. Pepsinogens are stored in intracellular granules and released by compound exocytosis. Stimulation of pepsinogen secretion begins its synthesis

in an autoregulatory manner. Upon release from chief cells, in acidic conditions below pH 5.0, pepsinogens are converted to pepsin, a proteolytic enzyme that is involved in food digestion. Pepsinogen secretion is also regulated by neural and cellular paracrine pathways. Pepsinogen secretion is stimulated by acetylcholine, CCK and neuropeptide substance P, via the increase in cellular Ca^{2+}, whereas secretin/VIP, histamine and beta adrenergic agent cause an increase in cAMP synthesis. In contrast, prostaglandin E2 and somatostatin decrease pepsinogen secretion by inhibition of cAMP synthesis.

The discovery of H. pylori-induced immune responses has added a new dimension to gastric physiology, as it has been shown that, in addition to bacterial products, inflammatory mediators – and their release in close proximity to parietal or regulatory cells – can modulate gastric secretion and motility and result in permanent aberrations of the gastric mucosa.

4. GASTRITIS

4.1 Introduction

The term gastritis has been used variously to describe symptoms referable to the upper gastrointestinal tract, the macroscopic appearances of inflammation or injury in the stomach at endoscopy and the histologic features of inflammation or injury to the gastric mucosa at microscopy. Unfortunately, there is poor correlation between an individual's symptoms and any abnormalities evident at endoscopy or microscopy. Upper gastrointestinal tract symptoms are best considered under the term dyspepsia while endoscopic features, such as erythema, hypertrophy, friability, petechial hemorrhages and erosions should be described as such and correlated with the histological features of inflammation and damage, which will be the subject of the present chapter.

Gastritis is defined as inflammation of the gastric mucosa (Figure 5), and the use of the term should therefore be based solely on an examination of gastric mucosal biopsies. Gastric mucosal biopsies should be obtained if there is endoscopic evidence of any mucosal abnormality, including erosions, ulcers, thickened folds, polyps or masses, or if there is a suspicion of H. pylori infection (Figure 6) or damage due to the ingestion of NSAIDs. Indeed, it has been proposed that an endoscopy performed without mucosal biopsies is an incomplete examination. In addition to specific lesions or abnormalities, biopsies should also be taken from the antrum (2 biopsies) and body of the stomach (2 biopsies) and some authors also recommend a fifth biopsy from the gastric angulus or incisura to identify possible H. pylori infection in patients who have recently received acid suppression therapy.

Strictly, the term 'gastritis' should be used only to describe changes characterized by a mucosal infiltrate of inflammatory cells while changes

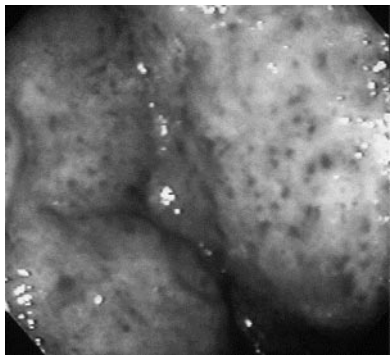

FIGURE 5. Fundal (Type A) gastritis.

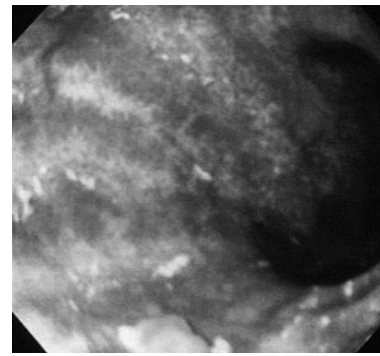

FIGURE 6. Chronic H. pylori gastritis.

attributable to the injurious effects of NSAIDs, alcohol and bile, for example, should be termed a chemical or reactive gastropathy. However, even a chemical gastropathy may be accompanied by inflammation and both entities will, therefore, be addressed.

Acute gastritis is characterized by an inflammatory infiltrate that is predominantly neutrophilic and is usually transient in nature. Inflammation may be accompanied by mucosal hemorrhage and superficial mucosa sloughing and, when severe, acute erosive gastritis may be associated with gastrointestinal bleeding (Figure 7). Acute gastritis may cause epigastric pain, nausea and vomiting but it may also be completely asymptomatic.

Chronic gastritis is characterized by an infiltrate of lymphocytes, plasma cells, or both, that may also be associated with intestinal metaplasia and atrophy of the epithelium. In intestinal metaplasia, the normal gastric epithelium is replaced by metaplastic columnar absorptive cells and goblet cells; these are usually small-intestinal in morphology although features of a colonic epithelium may be present. The development of atrophic gastritis and intestinal metaplasia is considered to be premalignant although the incidence of gastric cancer in gastric intestinal metaplasia is unknown and surveillance is not widely practised. In the Western world, histologic changes of chronic gastritis occur in up to 50% of the population in later life although the incidence of gastric cancer is falling, almost certainly due to the decreasing prevalence of H. pylori infection. Chronic gastritis rarely causes symptoms although it can be associated with nausea, vomiting and upper abdominal discomfort.

In addition to elements of chronicity, gastritis can also be categorized on the basis of identifiable etiology (e.g., infection, graft-versus-host disease, autoimmune, chemical gastropathy) or on the basis of histological appearance (e.g., granulomatous, eosinophilic, lymphocytic, hypertrophic)

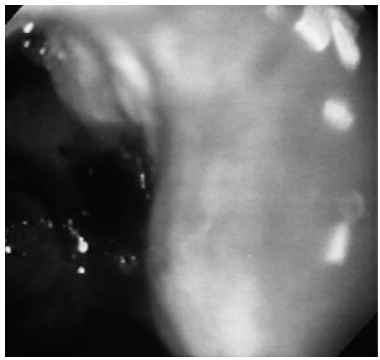

FIGURE 7. Bleeding ulcer at the site of a Billroth II anastomosis.

although, in practice, the categorization of gastritis may address both of these elements (Table 2).

4.2 Gastritides with Identifiable Etiology

4.2.1 INFECTIOUS GASTRITIDES

4.2.1.1 VIRAL

Cytomegalovirus (CMV) infection of the gastrointestinal tract usually occurs in immunocompromised individuals. CMV gastritis may be associated with epigastric pain and fever and the gastric mucosa may be edematous and congested, with erosions or ulceration at endoscopy. The characteristic histological finding is "owl-eye," intranuclear inclusions in cells of the mucosal epithelium, vascular endothelium and connective tissue.

Herpes infection with the H. simplex, H. varicella or H. zoster virus occurs by reactivation of a prior infection; again, this is seen most commonly in the immunocompromised patient, and leads to nausea, vomiting, fever, chills, fatigue and weight-loss. At endoscopy, the gastric mucosa has a cobblestone appearance due to multiple superficial linear ulcers and small raised ulcerated plaques, while histology shows numerous cells with ground-glass nuclei and eosinophilic, intranuclear inclusion bodies surrounded by halos.

4.2.1.2 BACTERIAL

H. pylori is the most common gastric bacterial infection worldwide and, surprisingly, it remained almost unrecognized until the seminal work of Barry Marshall and Robin Warren. The prevalence of H. pylori infection in the Western world is about 20-30% but its prevalence increases with age and, in the

TABLE 2. Gastritis classification

Gastritides with Identifiable Etiology
Infectious gastritis
Viral
Bacterial
H. pylori
Others, including Mycobacteria
Fungal
Parasitic
Graft-versus-host disease
Autoimmune gastritis
Chemical gastropathy
Medications
Aspirin, NSAIDs
Bisphosphonates, electrolytes (K^+)
Alcohol
Bile reflux
Ischemia
Cocaine, stress, atherosclerosis
Radiation
Trauma
Nasogastric or gastrostomy tubes
Bezoar
Prolapse / hiatal hernia
Gastritides Identifiable by Histological Appearance
Granulomatous gastritis
Crohn's disease
Sarcoidosis
Foreign bodies
Infections
Tumour-associated
Inflammatory infiltrate
Collagenous
Lymphocytic
Eosinophilic
Hypertrophic gastritis
Ménétrier's disease
Hyperplastic, hypersecretory gastropathy
Zollinger-Ellison syndrome
Miscellaneous gastritis
Gastritis cystica profunda

developing world, it may exceed 80%. H. pylori can be found in 90% of patients with chronic antral gastritis and most H. pylori-infected individuals have associated gastritis. Although many H. pylori-infected individuals have no symptoms, H. pylori is associated with an increased risk of developing peptic ulcer disease, gastric cancer and gastric 'MALT' lymphoma.

Although it initially causes antral gastritis, H. pylori may affect both antral and body-fundic mucosa. At endoscopy, the mucosa may appear coarse and reddened with thickened rugal folds but, with longer-standing infection, it may become thinned, flattened and atrophic. Chronic H. pylori gastritis is characterized by an infiltrate of lymphocytes and plasma cells in the lamina propria and lymphoid aggregates with germinal centres; a variable, active gastritis is characterized by neutrophils in the glandular and surface epithelial layer. H. pylori organisms reside in the superficial mucous layer, over the mucosal surface, and in gastric pits; they can usually be seen with a standard hematoxylin and eosin stain but special stains, such as the Warthin-Starry silver stain, acridine orange fluorescent stain and Giemsa stain may be needed if organisms are sparse.

Over time, the initial antral-predominant gastritis progresses to a pangastritis and then to atrophic gastritis and intestinal metaplasia – precursors to the development of gastric cancer (the "Correa hypothesis"). Eradication of H. pylori infection usually with regimens comprising two antibiotics and an acid antisecretory agent, is associated with a decreased risk of peptic ulceration and its complications and, probably, with a decreased risk of gastric cancer and gastric MALT lymphoma.

Phlegmonous (suppurative) gastritis is a rare bacterial infection of the submucosa and muscularis propria and is associated with massive alcohol ingestion, upper respiratory tract infection, and immune compromise; it has a mortality rate in excess of 50%. At endoscopy, the mucosa may show granular, green-black exudates and, at histology, there is an intense polymorphonuclear infiltrate with gram-positive and gram-negative organisms. Emphysematous gastritis, due to Clostridium welchii, may lead to the formation of gas bubbles, along the gastric contour on x-ray. Treatment requires gastric resection or drainage and high-dose systemic antibiotics.

Mycobacterium tuberculosis gastritis is rare; ulcers, masses, or gastric outlet obstruction may be seen at endoscopy and biopsies show necrotizing granulomas with acid-fast bacilli. Mycobacterium avium complex gastritis is very rare, even in immunocompromised individuals; gastric mucosal biopsies show foamy histiocytes containing acid-fast bacilli.

Actinomycosis and syphilis are very rare causes of gastritis, although the incidence of gastric syphilis has increased in the US over the last two decades. In actinomycosis, endoscopy may reveal appearances suggestive of a gastric

malignancy; biopsies show multiple abscesses containing Actinomyces israelii, a gram-positive filamentous anaerobic bacterium. In syphilis, endoscopy may show multiple serpiginous ulcers while biopsies show severe gastritis with a dense plasma cell infiltrate in the lamina propria, as well as some neutrophils and lymphocytes, gland destruction, vasculitis and granulomata.

4.2.1.3 FUNGAL AND PARASITIC

Candida and Histoplasma, the most common, albeit rare, fungal causes of gastritis are associated with impaired immune status; gastric phycomycosis (zygomycosis) is exceedingly rare but usually fatal. Parasitic causes of gastritis include Cryptosporidia, Strongyloides stercoralis, Anisakis (from raw marine fish), Ascaris lumbricoides and Necator americanus (hookworm).

4.2.2 GRAFT-VERSUS-HOST DISEASE (GVHD)

The stomach and esophagus are affected less often than small intestine and colon by GVHD, which usually follows allogeneic bone marrow transplantation. Acute GVHD occurs between days 21 and 100 after transplantation and, if it affects only the stomach, it is associated with nausea, vomiting and upper abdominal pain. Endoscopic findings are non-specific and histology shows cell necrosis (apoptotic bodies — intraepithelial vacuoles containing karyorrhectic debris and fragments of cytoplasm) in the neck region of the gastric mucosa.

4.2.3 AUTOIMMUNE GASTRITIS

Autoimmune gastritis, comprising less than 10% of chronic gastritis cases, is caused by one or more autoantibodies to parietal cell components, including intrinsic factor and the acid-producing proton pump (H^+,K^+ -ATPase). It is associated with other autoimmune disorders such as Hashimoto's thyroiditis and Addison's disease. Mucosal atrophy, with loss of parietal cells, leads to decreased production of acid and intrinsic factor; about 10% of these patients develop low serum vitamin B_{12} levels and pernicious anemia.

4.2.4 CHEMICAL GASTROPATHY (REACTIVE GASTROPATHY)

A number of different agents can produce gastric mucosal injury, characterized at endoscopy by hemorrhagic lesions and erosions (necrosis to the level of the muscularis mucosa) or ulcers (necrosis extending deeper than the muscularis mucosa). Biopsies show the typical changes of foveolar hyperplasia including an elongated, corkscrew appearance to the gastric pits, depletion of surface, mucin-containing cells, subepithelial hemorrhage and minimal inflammatory cell infiltrate.

Aspirin (ASA) and other NSAIDs are the most common causes of a chemical gastropathy; cyclo-oxygenase-2 selective inhibitors (COX-2 or coxibs)

are less likely to cause injury. Bile reflux gastritis has become far less common as partial gastrectomy (Billroth I and II) is now performed only rarely; however, bile gastritis also occurs after cholecystectomy or sphincteroplasty, or, occasionally, in the absence of prior surgery. Other causes of a chemical gastropathy include medications (e.g., potassium chloride supplements, bisphosphonates), alcohol, ischemia (chronic mesenteric insufficiency), cocaine, stress (in intensive care settings) and gastric bezoars. Portal hypertension produces a congestive gastropathy, with vascular ectasia but, again, only a minimal inflammatory infiltrate.

4.3 Gastritides Identified by Histological Appearance

4.3.1 GRANULOMATOUS GASTRITIDES

Crohn's disease is the most common cause of a granulomatous gastritis although the differential diagnosis includes sarcoidosis, foreign bodies, Churg-Strauss syndrome (granulomatous vasculitis), Whipple's disease, Langerhans cell histiocytosis (eosinophilic granuloma) and lymphoma.

Crohn's disease of the stomach is uncommon, particularly in the absence of disease elsewhere in the gastrointestinal tract. Endoscopy may show mucosal reddening and nodules with or without overlying erosions and ulcers that may be elongated or serpiginous. Histological features include non-caseating granulomata, ulceration, chronic inflammation and submucosal fibrosis. Sarcoidosis of the stomach can be difficult to distinguish endoscopically and histologically from Crohn's disease and the diagnosis must be based on the presence of other systemic features.

Xanthogranulomatous gastritis is characterized, histologically, by the presence of foamy histiocytes, inflammatory cells, multinucleated giant cells, and fibrosis and may extend into adjacent organs and simulate malignancy.

4.3.2 GASTRITIS WITH SPECIFIC FEATURES

Collagenous gastritis has been reported in association with collagenous colitis and lymphocytic colitis; it is very rare. At endoscopy, non-specific findings include mucosal hemorrhages, erosions and nodularity while histology shows a chronic gastritis (plasma cells and intra-epithelial lymphocytes), focal atrophy and focal collagen deposition (20–75 μm) in the lamina propria.

Lymphocytic gastritis is thought, by some, to be related to varioliform gastritis, which is associated with thick mucosal folds, nodularity and aphthous erosions at endoscopy. It has been described in association with H. pylori infection and, also, celiac disease (celiac sprue). Histology shows an infiltrate of the lamina propria in the antrum or body by plasma cells, lymphocytes and rare neutrophils, and a marked intraepithelial infiltrate with T lymphocytes.

TABLE 3. Differential diagnosis for intrinsic causes of thickened gastric folds

Lymphoma
Mucosa-associated lymphoid tissue (MALT) syndrome
Gastric adenocarcinoma
Linitis plastica
Ménétrier's disease
Acute H. pylori gastritis
Lymphocytic gastritis
Eosinophilic gastritis
Gastric varices
Gastritis cystica profunda
Gastric antral vascular ectasia
Kaposi's sarcoma
Zollinger-Ellison syndrome
Gastric Crohn's disease

Eosinophilic gastritis is associated with peripheral eosinophilia and eosinophilic infiltration of the stomach, involving one or more layers of the gastrointestinal tract (mucosa, muscle or subserosa). Endoscopy may show pylori obstruction, prominent gastric folds (Table 3), nodularity or ulceration, and histology is characterized by eosinophilic infiltration (> 20 per high power field), eosinophilic pit abscesses, necrosis and epithelial regeneration. Severe disease and symptoms may require corticosteroid therapy.

4.3.3 HYPERTROPHIC GASTROPATHIES

There are numerous causes of thickened gastric folds seen on endoscopy or diagnostic imaging (Table 3). Ménétrier's disease is associated with protein-losing gastropathy and hypochlorhydria whereas hyperplastic, hypersecretory gastropathy is associated with increased or normal acid secretion and hyperplasia of the parietal and chief cells, with or without protein loss. Endoscopy, in both cases, typically shows irregular hypertrophic folds involving the body of the stomach, although there is a polypoid variant that resembles multiple hyperplastic gastric polyps. The characteristic histological features are foveolar hyperplasia with cystic dilation; inflammatory infiltrates may be present, as in hypertrophic lymphocytic gastritis, but this is variable. Ménétrier's disease may resolve spontaneously; symptomatic treatment includes acid antisecretory agents (H2-RAs, PPIs), anticholinergics and a variety of other, empirical therapies, including octreotide and corticosteroids. Gastric resection for refractory protein loss, hemorrhage or obstruction is a last resort. Zollinger-Ellison syndrome, due to ectopic secretion of gastrin,

TABLE 4. Pathophysiologic defects in some patients with:

A. *Peptic ulcer disease/gastric ulcer disease*
Decreased acid secretion, decreased parietal cell mass (PCM), back-diffusion of acid
Chronic superficial and atrophic gastritis
Increased concentration of bile acids and pancreatic juice in stomach (duodenogastric reflux)
Delayed gastric emptying
Inappropriately decreased pyloric sphincter pressure under basal conditions and in response to acid (secretin) or fat (cholecystokinin) in the duodenum
B. *Duodenal ulcer disease*
Increased parietal cell mass
Increased sensitivity of parietal cells to gastrin and secretagogues
Increased secretory drive
Decreased acid-induced inhibition of meal-stimulated gastrin release
Increased gastric emptying
Increased duodenal acid/pepsin loads
Chronic active gastritis

responds well, symptomatically, to high-dose PPI therapy and, if a gastrinoma can be identified, surgery may be curative.

4.3.4 MISCELLANEOUS GASTRITIDES

Gastritis cystica profunda is a rare sequela of partial gastrectomy with gastrojejunostomy but it may also develop in the absence of prior gastric surgery. Endoscopy typically shows multiple exophytic gastric masses, which on section reveal multiple cysts. At histology, foveolar hyperplasia is accompanied by cystic glands that extend through the muscularis mucosae into the submucosa and muscularis propria. It may be associated with chronic atrophic gastritis, hyperplasia or primary gastric stump cancer after surgery.

5. PATHOPHYSIOLOGY OF PEPTIC ULCER DISEASE

Ulcer is defined as a break in the mucosa, which extends through the muscularis mucosae, and is surrounded by acute and chronic inflammation.

The lesion of peptic ulcer disease (PUD) is a disruption in the mucosal layer of the stomach or duodenum. An ulcer is distinguished from an erosion by its penetration of the muscularis mucosa or the muscular coating of the gastric or duodenal wall. Peptic ulcer diseases result from an imbalance between defensive mechanisms of the mucosa and aggressive factors.

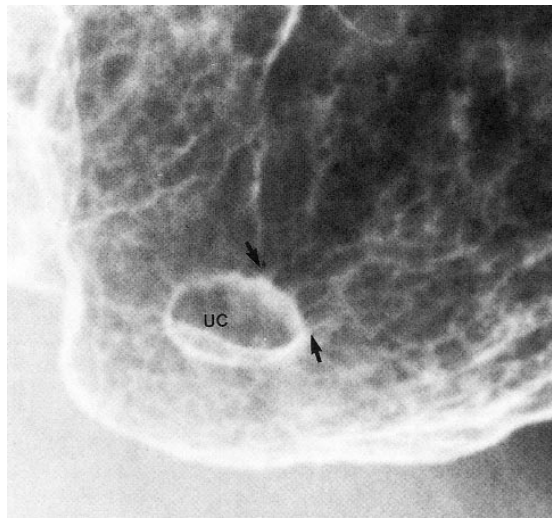

FIGURE 8. Benign gastric ulcer. Barium meal showing an ulcer crater (UC) situated on the greater curvature of the stomach, in the gastric antrum. The ulcer is visualized en face with a slightly oblique projection. Smooth mucosal folds radiating from the edge of the crater (arrows) in a regular fashion are a pathognomonic sign of a benign gastric ulcer. (Courtesy of Dr. J. Rawlinson.)

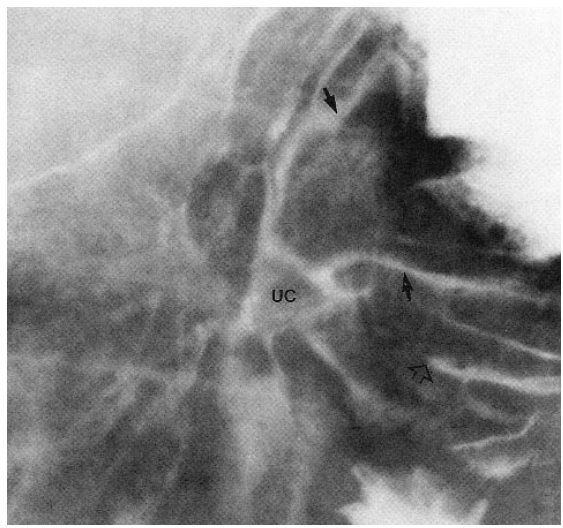

FIGURE 9. Malignant gastric ulcer. Barium meal demonstrating an ulcer crater (UC) on the lesseer curvature of the stomach, also visualized en face. In this case the radiating mucosal folds are irregularly thickened (e.g., between closed arrows) and do not extend to the edge of the crater (open arrow) – features indicating a local infiltrative, malignant process. (Courtesy of Dr. J. Rawlinson.)

A. Mucosal defence mechanisms
   - mucus secretion
   - bicarbonate production
   - mucosal blood flow
   - cellular repair mechanisms
   - prostaglandin E's
   - growth factors

B. Aggressive factors
   - acid/pepsin
   - bile acids
   - NSAIDs
   - H. pylori infection
   - cigarette smoking
   - EtOH, stresses, coffee

The etiology of peptic ulcer disease remains unclear, and there are numerous pathophysiologic defects (Table 4). Given the multiple processes that control acid and pepsin secretion and defence and repair of the gastroduodenal mucosa, it is likely that the cause of ulceration differs between individuals. Acid and pepsin appear to be necessary but not sufficient ingredients in the ulcerative process. It is clear that the majority of gastric ulcers (Figures 8, 9) and a substantial number of duodenal ulcers (Figures 10, 11, 12) do not have increased gastric acid secretion.

Peptic ulcers usually occur at or near mucosal transitional zones, areas that are particularly vulnerable to the deleterious effects of acid, pepsin, bile and pancreatic enzymes. Gastric ulcers are most commonly found on the lesser curvature, near the junction of acid-producing parietal cells and the antral mucosa, extending to an area 2–3 cm above the pylorus. Duodenal ulcers are usually found in the duodenal bulb, the pyloric channel or prepyloric area. Other peptic ulcers may occur in the esophagus, gallbladder (rarely, with ectopic gastric mucosa), and Meckel's diverticulum. Only one-third of DU patients have acid hypersecretion. Gastric acid production is relatively normal in patients with gastric ulcers.

The most important contributing factors are H. pylori infection, NSAIDs, acid and pepsin. NSAIDs can cause damage to the gastroduodenal mucosa via several mechanisms, including the topical irritant effect of these drugs on the epithelium, impairment of the barrier properties of the mucosa, suppression of gastric prostaglandin synthesis, reduction of gastric mucosal blood flow and interference with the repair of superficial injury (Figure 13). In addition, the presence of acid and, in some cases, H. pylori infection in the stomach and duodenum may contribute to the ability of NSAIDs to damage the mucosa.

In the absence of NSAIDs and gastrinoma, it appears that most gastric ulcers and all duodenal ulcers occur in the setting of H. pylori infection.

Evidence is mounting in support of H. pylori infection as a necessary factor in the ulcerative process, similar to acid and pepsin. It is not known whether the bacteria or the accompanying inflammation is the more important factor in the pathophysiology. Although the pathophysiology of gastric ulcer and duodenal ulcer is similar, there are clearly differences between the two

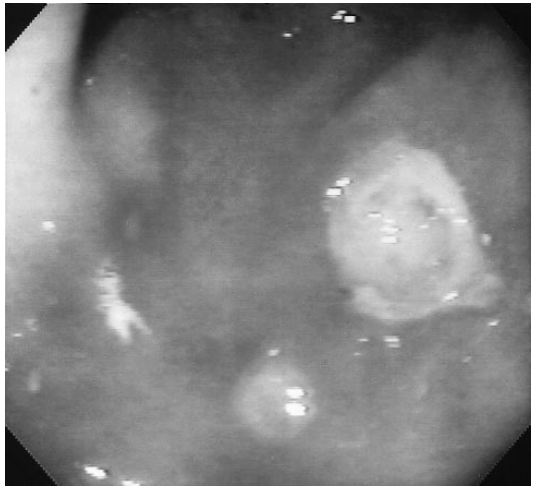

FIGURE 10. Duodenal ulcer, posterior wall.

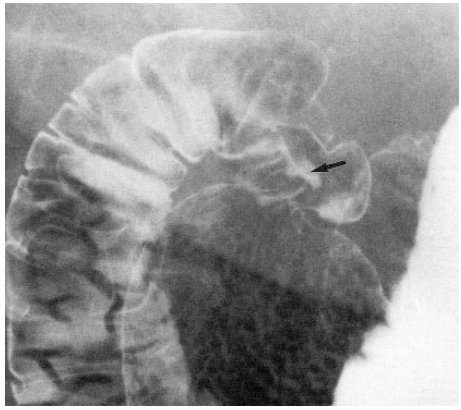

FIGURE 11. Duodenal ulcer situated at the base of the duodenal cap. The ulcer crater is filled with barium (arrow). The surrounding inflammatory process has considerably distorted the normal bulbar configuration of the proximal duodenum. (Courtesy of Dr. J. Rawlinson.)

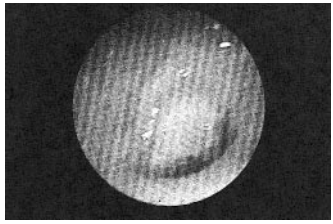

FIGURE 12. Duodenal ulcer. Endocopic view of the duodenal cap ulcer.

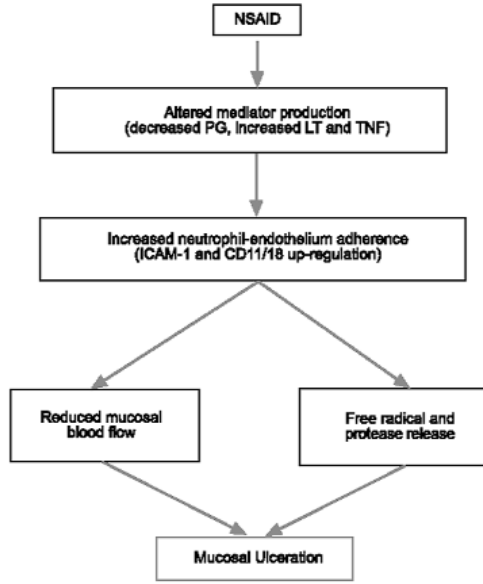

FIGURE 13. Role of changes in the gastric microcirculation in the pathogenesis of NSAID-induced ulceration. NSAIDs suppress prostaglandin (PG) synthesis, and cause an increase in the liberation of leukotriene (LT) B_4 and tumour necrosis factor (TNF). The net result is an increase in expression of various adhesion molecules, leading to neutrophil adherence to the vascular endothelium.

groups. Duodenal ulcer is typified by H. pylori infection and duodenitis and in many cases impaired duodenal bicarbonate secretion in the face of moderate increases in acid and peptic activity (Figure 14). The increased acid load resulting from H. pylori infection of the antrum is delivered to the duodenum, causing damage to the duodenal mucosa and eventually leading to the development of gastric metaplastic lesions. H. pylori bacteria can infect these islands of gastric mucosa, and the combination of increased acid delivery and H. pylori infection ultimately leads to ulcer formation (Figure 15). Gastric ulcer often occurs with decreased acid-peptic activity, suggesting that mucosal defensive impairments are more important (Figure 16).

5.1 Interaction Between H. pylori and NSAIDs

Although NSAID use and H. pylori infection are independent risk factors for peptic ulcer disease, there are conflicting data regarding the interaction of both factors on the disease. Some studies suggest that H. pylori infection does not increase the risk of peptic ulcer disease in patients taking NSAIDs. Other evidence suggests that it may increase the risk of both ulcers and bleeding complications in patients taking these drugs.

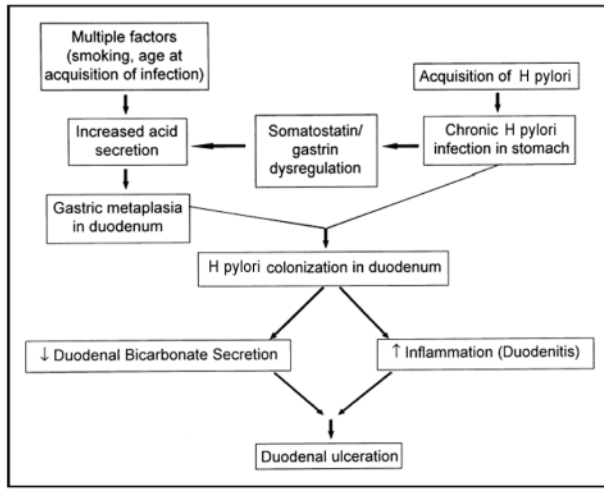

FIGURE 14. Model of duodenal ulcer pathogenesis. Persons infected with cagA/tox /H. pylori strains develop enhanced mucosal inflammation, which may lead to heightened gastric acid secretion with development of gastric metaplasia, colonization by H. pylori in the duodenum, and subsequent duodenal ulcer formation.

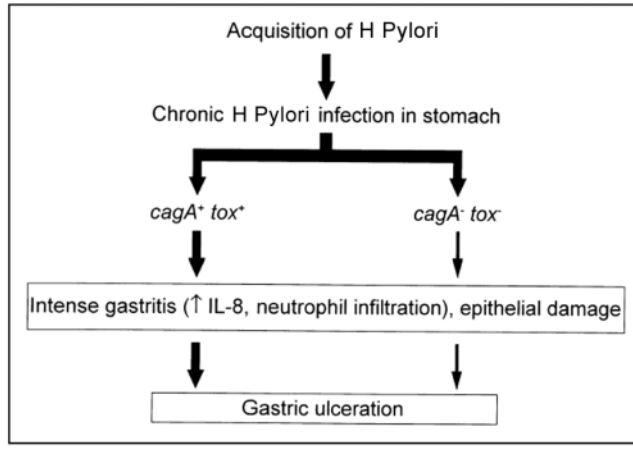

FIGURE 15. Model of ulcer pathogenesis. Persons harboring H. pylori strains that possess the cagA gene and have in vitro production of vacuolating cytotoxin (cagA/tox /) develop a more severe mucosal inflammatory response that may increase the risk of progression to ulceration.

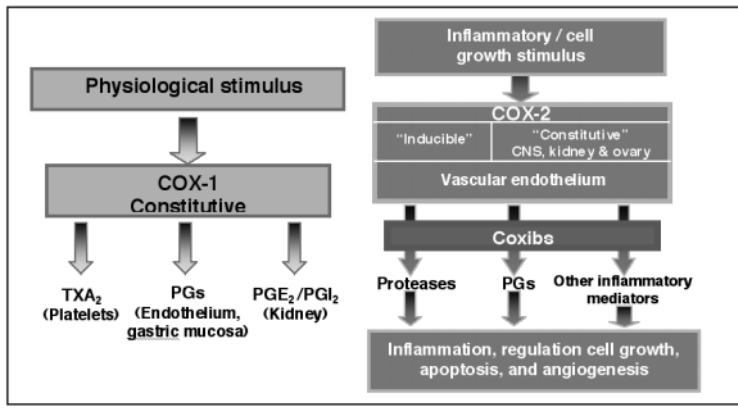

FIGURE 16. Proposed roles of the two known isoforms of COX and role of coxibs TXA_2, thrombozane A_2; PGE_2: prostaglandin E_2; PGs: prostaglandins; PGI_2: prostacycline; coxibs: COX-2 inhibitors.

The discovery of H. pylori has changed the life cycle of peptic ulcer disease (PUD). However, PUD does not completely disappear after elimination of H. pylori infection. Some ulcers recur even after successful eradication of H. pylori in non-NSAIDs users. In addition, the incidence of H. pylori-negative, non-NSAID PUD (idiopathic PUD) is reported to increase with time. Moreover, H. pylori-positive ulcers are not always H. pylori-induced ulcers because there are two paradoxes of the H. pylori story: the existence of H. pylori-positive non-recurring ulcer, and recurring ulcer after cure of H. pylori infection. Taken together, it is clear H. pylori infection is not the only cause of peptic ulcer disease. Therefore, it is still necessary to seriously consider the pathophysiology and the management of the ulcers, which may exist after elimination of H. pylori infection.

5.2 Predisposing Factors

Heredity plays some role in peptic ulcer diseases, especially in DU. Twenty to 50% of patients with DU have a positive family history for PUD. Inheritance patterns of DU and GU appear distinct (i.e., DU—>DU and GU—>GU). Studies of twins show greater concordance among identical than among fraternal twins. In addition, individuals with blood group O have about a 30% increased risk of DU, compared with those of other blood groups.

TABLE 5. Risk factors for serious GI events associated with NSAID use

Clinical risk factors	*Drug risk factors*	*Social risk factors*
Advance age	Individual NSAID risk	Smoking
History of ulcer or ulcer complications	High dose	Alcohol intake
Major illness (e.g., heart disease, type and severity of arthritis)	Multiple NSAIDs	
Severe comorbidity and disability	Concomitant corticosteroid	
H. pylori infection	Concomitant anticoagulant	

Duodenal ulcer is also associated with other illnesses such as hyperpepsinogenemia I, systemic mastocytosis, MEN I, G-cell hyperfunction, rapid gastric emptying, childhood duodenal ulcer and immunological forms of peptic ulcer disease, glucocorticoid, chronic renal failure, renal transplantation, cirrhosis, chronic obstructive lung disease, and neurological trauma and burns (Curling's ulcer).

6. NSAIDS AND GASTRIC DUODENAL DISEASES

Nonsteroidal anti-inflammatory drugs (NSAIDs) including aspirin are among the most widely prescribed effective drugs for the treatment of pain and inflammation. The use of NSAIDs, however, is a well-known cause of gastrointestinal (GI) adverse events, including dyspepsia, abdominal pain, nausea, erosive gastroduodenitis, ulceration, perforation, hemorrhage and even death. Nearly all patients who take aspirin or traditional NSAIDs develop asymptomatic acute upper GI tract injury (erosions or ulcers) at some point in time. Interestingly, very few patients who develop serious complications have antecedent dyspeptic symptoms. Treatment of GI events caused by NSAIDs is also costly. Studies have shown that for each dollar spent on NSAIDs, an additional 55–125% is needed to treat GI events. Risk factors for serious GI complications are outlined in Table 5.

The safety profile of NSAIDs is variable and dependent on the class of NSAID with the selective COX-2 inhibitor class being among the safest. Aspirin doses as low as 10 mg/day can cause ulcers. Long-term use of aspirin alone is associated with 1.5–3 times increase in risk of GI complications even when used at low-dose (≤ 150 mg daily) or buffered or as enteric-coated formulations. The use of traditional non-selective NSAIDs increases the risk of serious GI complications by approximately 2.5–5-fold compared with patients not receiving these medications. There is a 2–4-fold increase in risk

when low-dose aspirin is added to a non-selective NSAID compared to the use of low-dose aspirin alone. Among the classic NSAIDs, ibuprofen and etodolac are the least toxic. Naproxen, indomethacin, aspirin and diclofenac have intermediate toxicity, whereas ketoprofen and piroxicam are among the most toxic to the GI tract.

Although the mechanisms by which NSAIDs cause mucosal damage are not completely clear, they involve both topical injury and systemic effects. The complex elements that defend the gastroduodenal mucosa from damage are largely dependent on endogenous prostaglandins (PGs) synthesized in the GI mucosa. The two known isoforms of cyclo-oxygenase (COX), COX-1 and COX-2, direct the synthesis of PG from arachidonic acid. COX-1 is constitutively expressed in most cells and plays an important role in the GI mucosal protection, renal blood flow regulation and normal platelet function. In contrast, COX-2 is largely inducible by inflammation and is thought to generate prostaglandins that are responsible for pain and inflammation. In general, non-selective NSAIDs inhibit both COX-1 and COX-2 pathways leading to both beneficial (mucosal defense) and toxic outcomes. It has been postulated that the injurious effects of NSAIDs are due to the inhibition of COX-1 and loss of GI mucosal protection, and also due to increased risk of bleeding through inhibition of platelet function. There is a correlation between the risk of GI complications and the relative degree of inhibition of COX-1 and COX-2 isoenzymes. An NSAID with higher selectivity for COX-2 than COX-1 is associated with significantly less GI toxicity than other non-selective NSAIDs. The premise that preferential inhibition of COX-2 would maintain the therapeutic benefit of traditional NSAIDs with less GI toxicity due to sparing of COX-1 led to the development of more-selective COX-2 inhibitors. First generation coxibs (celecoxib and rofecoxib), and second generation coxibs (etoricoxib, valdecoxib, parecoxib and lumiracoxib) have improved GI tolerance and less adverse events across a range of different GI safety assessments. In clinical trials, coxibs significantly reduced the risk of ulcers and ulcer complications compared to non-selective NSAIDs.

The prevalence of ulcer complications such as upper GI hemorrhage has not declined in the past decade, although H. pylori infection is declining in our Canadian population. Ulcer complications remain, mainly because of the aging population and increasing prevalence of arthritis, which is leading to an increased consumption of NSAIDs. To protect patients at risk, several strategies are advised, including the use of the lowest effective dose of NSAIDs, concomitant use of gastroprotective agents (e.g., acid antisecretory drugs, proton-pump inhibitors, or mucosal protective drugs) or alternative treatment with a coxib. Prevention of GI events is in particular indicated among patients with risk factors who require long-term treatment with NSAIDs, and use of a

TABLE 6. Appropriate selection of NSAIDs and GI protective agents based on the key clinical factors

	Risk of GI NSAID event	
	Low	*Average / high*
Not on aspirin	NSAID alone	Coxib or NSAID+PPI
On aspirin	NSAID + PPI or coxib	NSAIDs +PPI or coxib +PPI

coxib and co-therapy with a PPI are the two most cost-effective treatments to decrease the risk of hospitalization for serious events (Table 6). The coxibs have decreased the risk of developing GI clinical events and complications in high-risk patients by more than 50% in large clinical trials. When economically possible, a coxib alone is preferable to a conventional NSAID plus a gastroprotective agent, but patients at high risk require a gastroprotective agent in addition to a coxib.

7. HELICOBACTER PYLORI AND PEPTIC ULCER DISEASE

7.1 Introduction

The discovery that H. pylori infection is the main cause of peptic ulcer caused a paradigm shift in our understanding of the disease pathogenesis. This was the first example of a common chronic bacterial infection usually acquired in childhood causing disease much later in life. In the future, many other diseases are likely to be linked to chronic infections but for now H. pylori studies provide fascinating insights into long term bacterial-host interactions.

7.2 Epidemiology

Individuals with a parent or sibling with gastric cancer are three times as likely to develop gastric cancer as the general population. People born in a country where gastric cancer is common (e.g., Japan or Eastern Europe) are also at increased risk, even if they have lived in North America for many years. Although regular screening is not warranted in either case, minor symptoms should be promptly and thoroughly investigated.

Studies around the world suggest the prevalence of H. pylori infection is 90–95% in patients with duodenal ulcer, 80–85% in patients with gastric ulcer and approximately 50% in the general population and 30% in Canada. Randomized controlled trial data proves that this association is causal but this does not mean that 90-95% of all duodenal ulcers are due to H. pylori. As the prevalence in the general population is also high, a few ulcers that are not due to H. pylori infection will still have the infection by chance. It is estimated that

about 75% of all peptic ulcers are attributable to H. pylori infection with most of the rest being due to non-steroidal anti-inflammatory drugs. The lifetime risk of having an ulcer in individuals infected with H. pylori is difficult to calculate, but is probably between 10 and 15%.

7.3 Pathophysiology

H. pylori infection is the most common chronic bacterial infection worldwide yet only a small proportion of cases develop disease. The reasons for this are not fully understood but relate to a combination of environmental, host and bacterial factors. Certain strains of H. pylori are more likely to cause peptic ulcer disease. The most well characterized is the cytotoxin associated gene (cagA) and the vacuolating cytotoxin (vacA) gene. The cagA gene encodes for a cagA protein that is injected into the host epithelial cells to induce changes in the gastric cytoskeleton. All strains possess the vacA gene but the s1m1 variant has the most potent cytotoxic activity and highest risk of causing peptic ulceration. Contact with epithelial (iceA) gene is another virulence factor with the iceA1 genotype, and is associated with increased gastric inflammation and higher likelihood of disease. Peptic ulceration is not universally present even with the most pathogenic strains of H. pylori and other factors such as male gender, host genetic factors (such as those that predict gastric acid output) and smoking will influence whether the infection causes disease.

Another epidemiological paradox is how an infection can cause both gastric and duodenal ulcer disease yet both types of ulcer rarely exist in the same patient. The distribution of infection in the stomach appears to be the most important determinant of disease phenotype. Duodenal ulceration most likely occurs when there is an antral predominant H. pylori infection that decreases antral somatostatin production. This reduces the negative inhibitory effect on gastrin production by antral G cells. The increased gastrin production increases parietal cell mass and acid output. The excess acid entering the duodenum causes the mucosa to undergo gastric metaplasia that can in turn be infected with H. pylori. The organism then causes inflammation, epithelial injury, and reduces duodenal bicarbonate secretion. This compromise to duodenal mucosal defence predisposes to ulcer formation.

In contrast, H. pylori infection is more likely to cause gastric ulceration if the infection is more evenly spread throughout the stomach. The pangastritis that results will cause inflammation of parietal cells and overall gastric acid secretion will be reduced. The inflammation will also impair mucosal defence and this can result in gastric ulceration even in a relatively hypochlorhydric environment.

The distribution of H. pylori is predicted by environmental factors. Acid output has yet to reach full capacity in the neonatal period so if H. pylori is

acquired soon after birth it will be able to infect the whole stomach causing a pan-gastritis. This is probably exacerbated by the poor nutrition seen in many developing countries. If the infection is acquired later in childhood when acid secretion is higher, H. pylori will prefer to reside in the antrum where less acid is produced.

7.4 Treatment of Peptic Ulcer Disease

Peptic ulcers can be healed by acid suppression but the disease usually recurs once anti-secretory therapy is discontinued. The strongest evidence that H. pylori infection causes peptic ulcer comes from randomized controlled trials that show eradication of the organism permanently cures the disease in most cases. Indeed antibiotic therapy alone can cure duodenal ulcer without the need for acid suppression. This evidence has led major guidelines worldwide to recommend H. pylori eradication therapy in infected patients with gastric and duodenal ulcer disease.

A systematic review of the literature has indicated that the relapse rate for duodenal ulcer disease after healing with acid suppression is 64% over 3–12 months. This fell to 14% in those receiving H. pylori eradication therapy. The relapse rate for gastric ulcer was 40% compared with 12% after H. pylori eradication. The number needed to treat (NNT) to prevent the recurrence of a duodenal ulcer was 2 (95% CI = 1.7 to 2.3). This is a very dramatic effect compared with the NNT for most other diseases but actually underestimates the true impact of H. pylori eradication, as many of the therapies included in the systematic review were substandard. When only proton pump inhibitor-based triple therapies or bismuth salt quadruple therapies were included, the relapse rate for duodenal ulcer patients fell to 8%. Many of the patients who relapsed still harboured H. pylori but a few patients had an ulcer relapse despite being H. pylori negative. This relates to the epidemiology of the association. If H. pylori is common, then a few patients will develop peptic ulcer disease through other causes and be infected by chance. Eradication of the organism in this setting will not cure the ulcer diathesis.

8. NON-VARICEAL GASTROINTESTINAL HEMORRHAGE

8.1 Introduction

Upper gastrointestinal hemorrhage is a common clinical problem, afflicting approximately one out of every thousand people each year. In most cases, bleeding stops spontaneously. However a minority rebleeds or continues to bleed despite attempts at hemostasis. This subpopulation accounts for most of the morbidity, mortality and resource consumption associated with upper gastrointestinal hemorrhage. Risk stratification allows targeted application of medical,

endoscopic and surgical therapy. Despite remarkable advances in each of these domains, however, approximately 1 in 20 patients who present with upper gastrointestinal bleeding will die over the course of their hospitalization.

8.2 Source of Hemorrhage

In most cases of upper gastrointestinal bleeding, a source is identified after careful clinical and endoscopic evaluation. In approximately 15% of cases, bleeding originates from esophageal or gastric varices associated with portal hypertension (discussed elsewhere). Among cases of non-variceal upper gastrointestinal hemorrhage, over 50% are caused by peptic ulcers. Other common sources of bleeding include erosive gastroduodenitis, esophagitis, Mallory-Weiss tears, angiodysplasia, Dieulafoy lesions and neoplasia.

8.3 Presentation and Risk Stratification

Bleeding from the upper gastrointestinal tract (proximal to the ligament of Treitz) manifests typically with overt hematemesis or coffee ground emesis, or with passage of melena per rectum. Brisk hemorrhage with rapid transit can present with maroon stool, hematochezia or features of hemodynamic instability. In all cases, the priority at initial assessment is to ensure hemodynamic stability and initiate appropriate volume resuscitation before conducting a detailed history and physical examination.

Key features of the history include: symptoms of hemodynamic instability (such as presyncope); prior upper gastrointestinal and liver disease with or without hemorrhage; other blood loss suggestive of an underlying bleeding diathesis; use of medications known to cause gastrointestinal injury (such as aspirin and NSAIDs); alcohol consumption; and family history of gastrointestinal pathology. On physical examination, key features include serial assessment of postural vital signs, thorough examination of the abdomen, careful inspection of the skin and mucus membranes for telangiectasia, assessment for the stigmata of chronic liver disease, and digital rectal examination. In all cases of overt hemorrhage, care must be taken to exclude respiratory or nasopharyngeal sources of blood loss. Passage of a nasogastric tube for aspirate can be informative; a biliary aspirate suggests a source of bleeding distal to the ampulla of Vater, while a bloody aspirate suggests a high-risk lesion and increased risk of mortality.

Upper gastrointestinal endoscopy (ideally within 24 hours of presentation) is a key component of patient assessment, and is often essential to diagnosis, prognosis and treatment. In most cases, an experienced endoscopist can localize the source of bleeding and estimate the risk of rebleeding. Of note, the Forrest classification of peptic ulcer stigmata (first reported in 1974) has withstood the test of time as a powerful predictor of

TABLE 7. Forrest classification of bleeding peptic ulcers and estimated risk of rebleeding

Risk Stratum:	*Forrest Grade:*	*Description:*	*Rebleed Risk:*
High	Ia	Active bleeding (spurting)	55%
	Ib	Active bleeding (oozing)	55%
	IIa	Visible vessel (non-bleeding)	43%
Intermediate	IIb	Adherent clot	22%
Low	IIc	Flat pigmented base	10%
	III	Clean fibrin base	5%

the risk of rebleeding (Table 7). By combining clinical and endoscopic criteria, clinicians can estimate risk with even greater accuracy. The Rockall score combines five domains (age, comorbidity, hemodynamic stability, bleeding source and Forrest classification) to predict rebleeding and mortality. Patients at low risk can be discharged home from the emergency department for outpatient follow-up.

8.4 Endoscopic Therapy

Endoscopic hemostatic therapy has been shown to reduce rebleeding, surgery and death among patients with high-risk endoscopic stigmata (Forrest classification Ia, Ib or IIa). Both injection therapy (saline +/- 10,000 epinephrine) and thermal coagulation therapy to ablate the bleeding vessel are effective. The combination of injection therapy plus thermal coagulation therapy is more effective than either intervention alone. In patients with adherent clots (Forrest classification IIb), management is controversial.

Aggressive irrigation to dislodge the clot and treatment of the underlying lesion is generally accepted. Clinical trials from expert centres have shown better outcomes when a cold snare is used to remove the clot, but many clinicians are reluctant to use this technique for fear of precipitating a brisk bleed. The use of endoscopic clips for hemostasis is a promising technique undergoing assessment in clinical trials.

For patients who rebleed after an initial attempt at endoscopic hemostasis, repeat endoscopy to reassess the lesion and apply further endoscopic treatment as needed is appropriate. However, routine second-look endoscopy in patients with no evidence of recurrent bleeding is not advocated.

8.5 Medical Therapy

Acid suppression can improve clot stability and platelet aggregation. Accordingly, medical therapy of non-variceal upper gastrointestinal hemorrhage is focused on achieving sustained and substantive elevation of gastric pH. Clinical trials of intravenous histamine-2-receptor antagonists have been disappointing, in part due to early induction of pharmacologic tolerance. However, an intravenous bolus of omeprazole followed by an intravenous infusion for 72 hours has been shown in several well-designed clinical trials to reduce the risk of rebleeding after endoscopy in patients with high-risk endoscopic lesions (Forrest classification Ia, Ib and IIa). Meta-analyses pooling these trials have also shown intravenous proton pump inhibitors to be associated with significant reductions in surgery and mortality.

Several controversies persist in the medical management of non-variceal upper gastrointestinal hemorrhage. First, the empiric use of proton pump inhibitors in patients prior to endoscopy has intuitive appeal but has not been tested in clinical trials. High doses of oral proton pump inhibitors may also be effective, but no rigorous head-to-head comparison with intravenous dosing has assessed clinical outcomes. Intravenous infusion of somatostatin analogs such as octreotide or vapreotide may also reduce rebleeding, and may be useful in patients with significant bleeding facing delays to endoscopy. Other agents such as tranexamic acid and recombinant factor VII can be considered in refractory patients, but have not been tested in clinical trials.

8.6 Surgery

Between 5% and 10% of patients who present with acute upper gastrointestinal bleeding will require surgery because of continued or recurrent hemorrhage. Although this proportion is gradually declining, it remains substantial as improvements in medical and endoscopic therapies are offset by the increasing age and comorbidity of patients admitted with gastrointestinal bleeding. The decision to perform surgery must be individualized, but consider factors such as patient comorbidity, transfusion requirements, the nature of the bleeding lesion and the anticipated success of further endoscopic therapy. Surgery should be considered early in patients at high risk of complications such as perforation (e.g., large, deep anterior duodenal ulcers).

8.7 Conclusions

Appropriate management of acute upper gastrointestinal hemorrhage entails early resuscitation and triage, careful clinical assessment, early endoscopy, intravenous proton pump inhibitors infusion (if indicated) and access to a skilled surgical team. Given the high prevalence of upper gastrointestinal

bleeding, each acute care hospital and health care system should develop institution-specific protocols for its management. These protocols should address aspects of triage and multidisciplinary care including access to a therapeutic endoscopist skilled in endoscopic hemostasis and trained support to assist with urgent endoscopy. Despite remarkable advances in medical and endoscopic therapy, non-variceal upper gastrointestinal hemorrhage continues to impose a significant disease burden.

9. GASTRIC MALIGNANCY

In the US over 20,000 new cases of gastric adenocarcinoma are diagnosed annually, with the majority detected at an advanced stage with 1- and 5-year survival rates of 30% and 10%, respectively. In Canada there were 2,800 new gastric cancer cases in 2001 (8 per 100,000) and 1,950 deaths.

The incidence of gastric adenocarcinoma (Figure 18) has been falling dramatically in North America from ~ 30 per 100,000 in the 1930s to 6–8 per 100,000 at present. There is a disparity in adenocarcinoma incidence between first- and second-generation immigrants, suggesting both genetic and lifestyle or environmental factors together contribute to the risk for cancer. Genetic factors that increase the risk include low gastric acid secretory status and the presence of pro-inflammatory genes such as interleukin-1ß, which is associated with gastric acid hyposecretion. Several lifestyle factors including diet and smoking increase the risk of gastric cancer but these are potentially modifiable. Infection with H. pylori is strongly associated with gastric malignancy and cancer develops in ≤ 1% of those infected.

9.1 Environmental Risk Factors for the Development of Gastric Adenocarcinoma

Environmental factors that contribute to gastric cancer include a high dietary salt and nitrate/nitrite intake, low fruit and vegetable intake, and the use of tobacco.

The INTERSALT Cooperative Research Group (39 populations, 24 countries) confirmed an association between stomach cancer mortality and 24-hour urinary sodium excretion, and 24-hour urinary nitrate excretion, in both men and women.

Dietary studies show that subjects with the highest intake of vegetables have a significantly reduced risk of gastric cancer compared to those who consume no vegetables. Similar but weaker protective effects have also been observed for consumption of green and cruciferous vegetables.

Several studies confirm that current smoking adversely influences the risk for gastric cancer and risk increases with the intensity and duration of cigarette smoking.

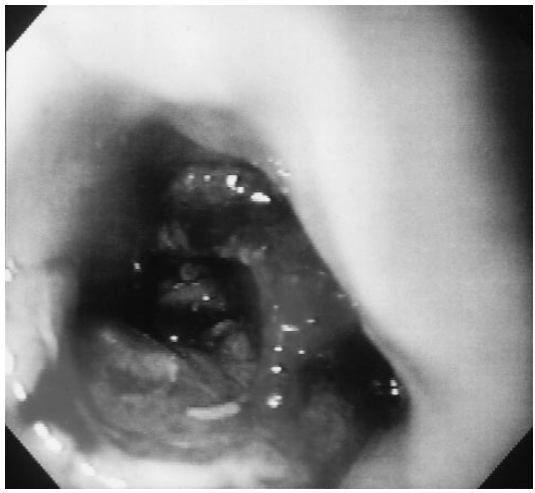

FIGURE 18. Carcinoma of the gastric cardia.

9.1.1 HELICOBACTER PYLORI INFECTION, DURATION, AND GENOTYPES-RISK FACTORS FOR GASTRIC CANCER

In 1994, the International Agency for Research on Cancer (WHO) classified H. pylori as a group 1 carcinogen based on numerous studies that confirmed the association between H. pylori infection and gastric cancer rather than by direct cause and effect. Nested case-control studies showed an increase in the risk of cancer (odds ratios 2.5–6.0) while meta-analyses of cohort or case-controlled studies reported summary odds ratios for gastric cancer in those infected with H. pylori of 1.92–2.24. Younger individuals had a higher risk for gastric cancer than older patients.

9.2 Gastritis, Intestinal Metaplasia and Gastric Cancer

Almost a decade before H. pylori was isolated, Correa proposed the concept of an inflammatory cascade initiated by an acute gastritis progressing to a chronic atrophic gastritis as the basis for gastric carcinogenesis. It is now clear that H. pylori infection is the most common cause of chronic gastritis. In a proportion of patients with chronic atrophic gastritis, intestinal metaplasia develops and, in a much smaller proportion, dysplasia and subsequently cancer. Recent studies have shown the importance of inflammation, arising from the initial H. pylori infection with resultant gene polymorphisms, which increase the risk of gastric cancer. Patients with the interleukin-1 gene cluster polymorphism, which may enhance production of the proinflammatory

cytokine interleukin-1β, are at increased risk of H. pylori-induced hypochlorhydria and gastric cancer. Thus, host genetic factors that affect interleukin-1ß production and hypochlorhydria may influence gastric cancer risk in those infected with H. pylori. In relatives of index cases of gastric cancer who had H. pylori infection, atrophy and hypochlorhydria were significantly more common than in non-infected relatives.

The presence of other pro-inflammatory polymorphisms, including interleukin-1β, interleukin-1 receptor antagonist, tumour necrosis factor-α and interleukin-10, confer an increasingly greater cancer risk. Such exciting advances in the genetics of gastric cancer promise a means to identify early those who are at risk of this serious malignancy.

9.3 Diagnosis of Gastric Cancer

Diagnosis of gastric cancer should be suspected in patients over the age of ~ 50 years with epigastric symptoms of new onset, including early satiety, anorexia, nausea and vomiting, and especially when there are associated alarm symptoms of anemia, weight loss etc. However, by this stage the disease is likely to be advanced. Confirmatory diagnosis is usually made at endoscopy when biopsies and the intraluminal extent can be determined. Routine barium meal is of little value in diagnosis although the tumour will invariably be seen. Ultrasound may sometimes be helpful and abdominal CT scan can be used to determine the extent of disease and any metastatic spread. Gastric cancer may spread within the abdomen, for example to the ovaries (Krukenburg tumour).

9.4 Staging of Gastric Cancer

Staging of the tumour is usually undertaken to determine prognosis and progress of the cancer. The widely used TNM (Tumour, Node, Metastasis) system is usually used and can help decide on the best course of treatment. Staging determines characteristics of the tumour and the extent of spread to other parts of the body.

9.5 Treatment of Gastric Cancer

Treatment of gastric cancer is usually surgical, although a palliative endoscopic procedure with tumour debulking may be considered in patients unfit for a definitive procedure. Surgical approaches involve partial, or sometimes total, gastrectomy depending on the location and extent of the tumour. The procedure may also involve removal of any lymph nodes involved in the malignancy. The more radical procedures will involve complex anastomosis

to maintain continuity of the gut and esophago-jejunal anastomosis in the case of total gastrectomy. Careful long-term follow up of such patients is essential to maintain optimal nutritional status.

Radiation therapy and chemotherapy may also be used depending on the extent and stage of the tumour. Current chemotherapeutic agents may include epirubicin, cisplatin, 5-fluorouracil while the newer generation of chemotherapeutic agents, such as gemcitabine, irinotecan and paclitaxel and the recent introduction of "biological" or immunological treatments or vaccines, which block growth signals, inhibit angiogenesis, stimulate the bodies own immune system etc., offer new hope for patients with a condition that has traditionally carried a very poor outlook.

9.6 Gastric Cancer Prevention

A healthy diet, rich in fruits and vegetables and low in salt, pickles, nitrates and nitrites is likely to carry a reduced risk of gastric cancer. It is not clear to what extent heredity is important although numerous reports of familial gastric cancer are documented. The common originating factor may still be infection with H. pylori in a household. The new information on genetics mentioned above will help clarify this. An important question that is not yet answered is whether widespread eradication of (or vaccination against) H. pylori infection will reduce or prevent gastric cancer. A large number of trials with differing endpoints is under way but it seems clear that treatment would need to be given relatively early in life before intestinal metaplasia and dysplasia have occurred for cancer to be prevented. Guidelines in Canada recommend that H. pylori infection be eradicated whenever detected.

9.7 Other Gastric Malignancies

Gastric lymphoma is a rare tumour representing between 2 and 7% of gastric malignancies. Lymphoma may be primary or secondary from a more generalized lymphoma arising in other organs.

The primary mucosa-associated lymphoid tissue lymphoma (MALT) is increasingly recognized and may also be associated with H. pylori infection. Treatment may lead to remission of the disease but the patient remains at risk of a recurrence in the event of reinfection.

Secondary lymphoma must be managed as part of the systemic disease.

The stomach may be involved in familial adenomatous polyposis, and in patients in whom this is detected in the rectum and colon, a full gastrointestinal survey with endoscopy and radiology is necessary with appropriate ongoing surveillance where indicated.

10. OTHER GASTRIC DISEASES

10.1 Acute

Gastric volvulus is a rare cause of acute upper abdominal pain and vomiting and can be partial (antral) or total (entire stomach). These obstructions can arise by themselves, or as torsion within a hiatus hernia. Volvulus within a hernia is not uncommon in the elderly and may be asymptomatic. The belief that twisting obstruction poses an important risk to the blood supply is probably unjustified. Gastric aspiration is followed by surgical relief of the volvulus in those who present with obstruction.

Sudden gross gastric distention and acute dilation of the stomach can arise after any form of upper abdominal surgery, including cholecystectomy, and especially after vagotomy, after childbirth and in diabetic coma. The causes are uncertain. Vomiting of relatively clear gastric contents is succeeded by the production of dirty brown or feculent material and the development of abdominal distention. Prompt decompression with a large-bore stomach tube and intravenous fluid replacement are required. After a variable interval the condition should then resolve spontaneously.

Gastric rupture is a rare, acute, nontraumatic, spontaneous rupture of the stomach, which is catastrophic and poorly understood. The majority of ruptures occur on the lesser curvature. They have also been reported to occur during upper gastrointestinal radiography using barium, sodium bicarbonate ingestion, nasal oxygen therapy, cardiopulmonary resuscitation and labour, and during the postpartum period.

10.2 Chronic

Hypertrophic pyloric stenosis is an idiopathic condition that may occur in infants or adults. The muscle of the pyloric canal is unduly hypertrophied. Infantile hypertrophic pyloric stenosis is more common in boys than in girls (the sex ratio is approximately 10:1), is a frequent anomaly (its incidence is about 3 per 1,000 live births) and is thought to be due to a combination of genetic predisposition and some abnormality of fetal or early postnatal development. Symptoms usually develop in the first few weeks after birth and characteristically consist of copious projectile vomiting of the gastric contents after feeding. On examination there is usually visible gastric peristalsis; a lump can be felt abdominally in the region of the pylorus. Barium-meal examination is not usually necessary but will confirm the presence of a narrow segment, 1–2 cm long, at the pylorus. The condition must be distinguished clinically from esophageal atresia (which involves difficulties with swallowing, with onset at birth) and duodenal obstruction/atresia (which involves bile-stained vomitus). A minor

proportion of all cases settle in the first two to three months with conservative management with anticholinergic drugs, but most patients will require early surgery with Ramstedt's procedure (pyloromyotomy).

Gastric polyps are gastric epithelial or non-epithelial protrusions observed either endoscopically or radiologically. The non-epithelial polyps arise from the mesenchymal tissue of the submucosa (such as a leiomyoma). The epithelial polyps are most common, and are often multiple, hyperplastic polyps. Infrequently, adenomatous or villoadenomatous polyps, which are often singular, occur. Duodenal adenomatous polyps may also be found in patients with Familial Adenomatous Polyposis (FAP) Syndrome.

Gastric diverticula occur most commonly near the cardia on the lesser curve, but occasionally are found in the prepyloric region. They seldom cause symptoms. Their principal importance lies in the likelihood of confusion with gastric ulceration on barium radiography.

Pseudolymphoma is localized lymphoid hyperplasia of the stomach. The lesions are raised, flat or nodular folds, and are often associated with gastric ulceration. The etiology of this condition remains unclear, but H. pylori infection has been implicated. It is difficult to exclude lymphoma using radiology or endoscopic biopsy, thus, a resected specimen is required for diagnosis.

Gastric bezoars are persistent concretions found in the stomach and consist of a variety of substances, most commonly plant and vegetable fibres (phytobezoars), persimmons (disopyrobezoars) or hair (trichobezoars). They most commonly occur in patients with previous gastric surgery or delayed gastric emptying and often produce symptoms including early satiety, abdominal fullness and epigastric pain. They may also occur in patients with behavioural disorders and the mentally challenged, especially when institutionalized. They can be complicated by gastric ulcer, secondary anemia and bleeding. Treatment methods include endoscopic removal or destruction, oral enzymatic therapy to dissolve the bezoar and metoclopramide.

SUGGESTED READING LIST

Barkun A, Bardou M, Marshall JK. Consensus recommendations for managing patients with nonvariceal upper gastrointestinal bleeding. Ann Intern Med 2003; 139:843-857.

Chan FKL, Leung WK. Peptic-ulcer disease. Lancet 2002; 360:933-941.

Cook DJ, Guyatt GH, Salena BJ, Laine LA. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. Gastroenterology 1992; 102:139-148.

Delaney B, Moayyedi P, Forman D. *Helicobacter pylori* infection. Clin Evid 2002; 8:453-468.

Dubois RW, Melmed GY, Henning JM, Laine L. Guidelines for the appropriate use of non-steroidal anti-inflammatory drugs, cyclo-oxygenase-2-specific inhibitors and proton pump inhibitors in patients requiring chronic anti-inflammatory therapy. Aliment Pharmacol Ther 2004; 19:197-208.

Ford AC, Delaney BC, Forman D, Moayyedi P. Eradication therapy in *Helicobacter pylori* positive peptic ulcer disease: systematic review and economic analysis. Am J Gastroenterol 2004; 99:1833-1855.

Forrest JA, Finlayson ND, Shearman DJ. Endoscopy in gastrointestinal bleeding. Lancet 1974; 2:394-397.

Hawkey CJ, Langman MJ. Non-steroidal anti-inflammatory drugs: overall risks and management. Complementary roles for COX-2 inhibitors and proton pump inhibitors. Gut 2003; 52:600-608.

Hunt RH, Barkun AN, Baron D, et al. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol 2002; 16:231-240.

Hunt RH, Fallone C, Veldhuyzen van Zanten S, Sherman P, Smaill F, Thomson AB. Canadian Helicobacter Study Group. Risks and benefits of *Helicobacter pylori* eradication: current status. Can J Gastroenterol 2002; 16:57-62.

Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994; 331:717-727.

Lau JY, Sung JJ, Lee KK, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. N Engl J Med 2000; 343:310-316.

Parsonnet J. *Helicobacter pylori*: the size of the problem. Gut 1998; 43(Suppl 1):S6-S9.

Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal hemorrhage. Gut 1996; 38:316-321.