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 Clinical examination of the gastrointestinal tract Observation Hands Clubbing Koilonychia Signs of liver disease (Ch. 22) Head and neck Pallor Jaundice Angular stomatitis Glossitis Parotid enlargement Mouth ulcers Dentition Lymphadenopathy Abdominal examination (see opposite) Multiple surgical scars, a prolapsing ileostomy and enterocutaneous fistulae in a patient with Crohn’s disease • Distressed/in pain? • Fever? • Dehydrated? • Habitus • Skin Skin and nutritional status Muscle bulk Signs of weight loss Groin Herniae Lymph nodes Perineum/rectal (see opposite) Fistulae Skin tags Haemorrhoids Masses Clubbing in patient with malabsorption Virchow’s gland in gastric cancer Pyoderma gangrenosum in ulcerative colitis Atrophic glossitis and angular stomatitis in vitamin B12 deficiency Observe Distension Respiratory movements Scars Colour Palpate Tender/guarding Masses Viscera Liver (Ch. 22) Kidneys (Ch. 15) Spleen Percuss Ascites Viscera Auscultate Bowel sounds Bruits

Tumour Polyp Cancer Extrinsic Tumour Abscess Prostate Uterus/cervix Prolapse Stool Consistency Colour Steatorrhoea Bloody/black Faecal occult blood Anal disease Tags Haemorrhoids Polyps Crohn’s disease 6 Rectal examination: common findings Epigastric mass Gastric cancer Pancreatic cancer Aortic aneurysm Left upper quadrant mass ?Spleen Edge Can’t get above it Moves towards right iliac fossa Dull percussion note Notch ?Kidney Rounded Can get above it Moves down Resonant to percussion Ballotable Tender to palpation ?Peritonitis Guarding and rebound Absent bowel sounds Rigidity ?Obstruction Distended Tinkling bowel sounds Visible peristalsis Left iliac fossa mass Sigmoid colon cancer Constipation Diverticular mass Right iliac fossa mass Caecal carcinoma Crohn’s disease Appendix abscess Hepatomegaly Palpable gallbladder (Ch. 22) Generalised distension Fat (obesity) Fluid (ascites) Flatus (obstruction/ileus) Faeces (constipation) Fetus (pregnancy) Suprapubic mass Bladder Pregnancy Fibroids/carcinoma 4 Abdominal examination: possible findings

766 • GASTROENTEROLOGY Functional anatomy and physiology Oesophagus, stomach and duodenum The oesophagus is a muscular tube that extends 25 cm from the cricoid cartilage to the cardiac orifice of the stomach. It has an upper and a lower sphincter. A peristaltic swallowing wave propels the food bolus into the stomach (Fig. 21.1). The stomach acts as a ‘hopper’, retaining and grinding food, and then actively propelling it into the upper small bowel (Fig. 21.2). Diseases of the gastrointestinal tract are a major cause of morbidity and mortality. Approximately 10% of all GP consultations in the UK are for indigestion and 1 in 14 is for diarrhoea. Infective diarrhoea and malabsorption are responsible for much ill health and many deaths in the developing world. The gastrointestinal tract is the most common site for cancer development. Colorectal cancer is the third most common cancer in men and women and population-based screening programmes exist in many countries. Functional bowel disorders affect up to 10–15% of the population and consume considerable health-care resources. The inflammatory bowel diseases, Crohn’s disease and ulcerative colitis, together affect 1 in 250 people in the Western world, with substantial associated morbidity. Fig. 21.1 The oesophagus: anatomy and function. The swallowing wave. Swallowing begins as a voluntary process. The food bolus is forcibly propelled by the tongue into the pharynx The upper oesophageal sphincter relaxes Peristaltic activity, controlled by a brainstem centre, is mediated by autonomic nerves The lower oesophageal sphincter relaxes. The food enters the stomach

Upper sphincter (cricopharyngeus muscle) Lower oesophageal sphincter Endoscopic view Normal high-resolution manometry Fig. 21.2 Normal gastric and duodenal anatomy. Vagus nerves Cardia Fundus Antrum Body Pancreas First part of duodenum Second part of duodenum Common bile duct Endoscopic view Endoscopic view Third part of duodenum Diaphragm

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duodenal mucosa from the ulcerative properties of acid and pepsin. Small intestine The small bowel extends from the ligament of Treitz to the ileocaecal valve (Fig. 21.4). During fasting, a wave of peristaltic activity passes down the small bowel every 1–2 hours. Entry of food into the gastrointestinal tract stimulates small bowel peristaltic activity. Functions of the small intestine are: • digestion (mechanical, enzymatic and peristaltic) • absorption – the products of digestion, water, electrolytes and vitamins • protection against ingested toxins • immune regulation. Gastric secretion Gastrin, histamine and acetylcholine are the key stimulants of acid secretion. Hydrogen

and chloride ions are secreted from the apical membrane of gastric parietal cells into the lumen of the stomach by a hydrogen–potassium adenosine triphosphatase (ATPase) (‘proton pump’) (Fig. 21.3). The hydrochloric acid sterilises the upper gastrointestinal tract and converts pepsino gen, which is secreted by chief cells, to pepsin. The glycoprotein intrinsic factor, secreted in parallel with acid, is necessary for vitamin B12 absorption. Gastrin, somatostatin and ghrelin The hormone gastrin is produced by G cells in the antrum, whereas somatostatin is secreted from D cells throughout the stomach. Gastrin stimulates acid secretion and mucosal growth while somatostatin suppresses it. Ghrelin, secreted from oxyntic glands, stimulates acid secretion but also appetite and gastric emptying. Protective factors Bicarbonate ions, stimulated by prostaglandins, mucins and trefoil factor family (TFF) peptides, together protect the gastroFig. 21.3 Control of acid secretion. Gastrin released from antral G cells in response to food (protein) binds to cholecystokinin receptors (CCK-2R) on the surface of enterochromaffin-like (ECL) cells, which in turn release histamine. The histamine binds to H2 receptors on parietal cells and this leads to secretion of hydrogen ions in exchange for potassium ions at the apical membrane. Parietal cells also express CCK-2R and it is thought that activation of these receptors by gastrin is involved in regulatory proliferation of parietal cells. Cholinergic (vagal) activity and gastric distension also stimulate acid secretion; somatostatin, vasoactive intestinal polypeptide (VIP) and gastric inhibitory polypeptide (GIP) may inhibit it. (ACh-R = acetylcholine receptor; ATPase = adenosine triphosphatase) Enterochromaffin-like cell Parietal cell Histamine Gastrin CCK-2R Gastrin CCK-2R H2 ACh-R (M3) Vagal stimulation Anticipation or smell of food Gastric distension H+/K+ ATPase K+ H+ Cl– Fig. 21.4 Small intestine: anatomy. Epithelial cells are formed in crypts and differentiate as they migrate to the tip of the villi to form enterocytes (absorptive cells) and goblet cells. Superior mesenteric artery Jejunum Arteries Veins Lymphatics Paneth cells Ligament of Treitz Brush border microvilli Crypts Villi Ileum

 energy-requiring process involving a carrier protein, and fructose enters by simple diffusion. Protein The steps involved in protein digestion are shown in Figure 21.6. Intragastric digestion by pepsin is quantitatively modest but important because the resulting polypeptides and amino acids stimulate cholecystokinin (CCK) release from the mucosa of the proximal jejunum, which in turn stimulates release of pancreatic proteases, including trypsinogen, chymotrypsinogen, pro-elastases and procarboxypeptidases, from the pancreas. On exposure to brush border enterokinase, inert trypsinogen is converted to the active proteolytic enzyme trypsin, which activates the other pancreatic pro-enzymes. Trypsin digests proteins to produce oligopeptides, peptides and amino acids. Oligopeptides are further hydrolysed by brush border enzymes to yield dipeptides, tripeptides and amino acids. These small peptides and the amino acids are actively transported into the enterocytes, where intracellular peptidases further digest peptides to amino acids. Amino acids are then actively transported across the basal cell membrane of the enterocyte into the portal circulation and the liver. Digestion and absorption Fat Dietary lipids comprise long-chain triglycerides, cholesterol esters and lecithin. Lipids are insoluble in water and undergo lipolysis and incorporation into mixed micelles before they can be absorbed into enterocytes along with the fat-soluble vitamins A, D, E and K. The lipids are processed within enterocytes and pass via lymphatics into the systemic circulation. Fat absorption and digestion can be considered as a stepwise process, as outlined in Figure 21.5. Carbohydrates Starch is hydrolysed by salivary and pancreatic amylases to: • α-limit dextrins containing 4–8 glucose molecules • the disaccharide maltose • the trisaccharide maltotriose. Disaccharides are digested by enzymes fixed to the microvillous membrane to form the monosaccharides glucose, galactose

and fructose. Glucose and galactose enter the cell by an Fig. 21.5 Fat digestion. Step 1: Luminal phase. Fatty acids stimulate cholecystokinin (CCK) release from the duodenum and upper jejunum. The CCK stimulates release of amylase, lipase, colipase and proteases from the pancreas, causes gallbladder contraction and relaxes the sphincter of Oddi, allowing bile to flow into the intestine. Step 2: Fat solubilisation. Bile acids and salts combine with dietary fat to form mixed micelles, which also contain cholesterol and fat-soluble vitamins. Step 3: Digestion. Pancreatic lipase, in the presence of its co-factor, colipase, cleaves long-chain triglycerides, yielding fatty acids and monoglycerides. Step 4: Absorption. Mixed micelles diffuse to the brush border of the enterocytes. Within the brush border, long-chain fatty acids bind to proteins, which transport the fatty acids into the cell, whereas cholesterol, short-chain fatty acids, phospholipids and fat-soluble vitamins enter the cell directly. The bile salts remain in the small intestinal lumen and are actively transported from the terminal ileum into the portal circulation and returned to the liver (the enterohepatic circulation). Step 5: Re-esterification. Within the enterocyte, fatty acids are re-esterified to form triglycerides. Triglycerides combine with cholesterol ester, fat-soluble vitamins, phospholipids and apoproteins to form chylomicrons. Step 6: Transport. Chylomicrons leave the enterocytes by exocytosis, enter mesenteric lymphatics, pass into the thoracic duct and eventually reach the systemic circulation. Simple micelles Enterohepatic circulation Pancreatic enzyme secretion Gallbladder contraction C V P Digestion of triglycerides C V P C V P Apoproteins Absorption Chylomicrons Bile acids resorbed in terminal ileum

Fat emulsification by motor activity CCK release from duodenum Dietary fat Fat solubilisation (‘mixed’ micelles) Bile acids and salts Fat Lipase Colipase Monoglycerides Free fatty acids Triglycerides Lymphatics Enterocyte Triglyceride Glycerol Fatty acids Cholesterol (C) Phospholipids (P) Vitamins A, D, E and K (V)

Fig. 21.6 Protein digestion. (CCK = cholecystokinin) CCK release Minor digestion by pepsins Trypsinogen Enterokinase Trypsin Proteins Activation of other pro-enzymes Peptides Amino acids Oligopeptides Brush border enzymes Small peptides Amino acids Enterocyte Peptides Peptidase Amino acids Portal circulation Liver Peptides Peptidase Amino acids Stomach Small intestine Pancreas Pancreatic pro-enzyme secretion Fig. 21.7 Fluid homeostasis in the gastrointestinal tract. Saliva 1500 mL Gastric 2000 mL Pancreas 1500 mL Small intestine 1500 mL 100 mL Food + H_2O intake 1200 mL Bile 500 mL Colonic reabsorption 1400 mL Portal vein 6700 mL Total in Reabsorbed Stool excretion 8200 mL 8100 mL 100 mL Water and electrolytes Absorption and secretion of electrolytes and water occur throughout the intestine. Electrolytes and water are transported by two pathways: • the paracellular route, in which passive flow through tight junctions between cells is a consequence of osmotic, electrical or hydrostatic gradients • the transcellular route across apical and basolateral membranes by energy-requiring specific active transport carriers (pumps). In healthy individuals, fluid balance is tightly controlled, such that only 100 mL of the 8 litres of fluid entering the gastrointestinal tract daily is excreted in stools (Fig. 21.7). Vitamins and trace elements Water-soluble vitamins are absorbed throughout the intestine. The absorption of folic acid, vitamin B12, calcium and iron is described on page 943. Protective function of the small intestine Physical defence mechanisms There are several levels of defence in the small bowel (Fig. 21.8). Firstly, the gut lumen contains host bacteria (see below), mucins and secreted antibacterial products, including defensins and immunoglobulins that help combat pathogenic infections.

Secondly, epithelial cells have relatively impermeable brush border membranes and passage between cells is prevented by tight and adherens junctions. These cells can react to foreign peptides (‘innate immunity’) using pattern recognition receptors found on cell surfaces (Toll receptors) or intracellularly. Lastly, in the subepithelial layer, immune responses occur under control of the adaptive immune system in response to pathogenic compounds. Immunological defence mechanisms Gastrointestinal mucosa-associated lymphoid tissue (MALT) constitutes 25% of the total lymphatic tissue of the body and is at the heart of adaptive immunity. Within Peyer’s patches,

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Lumen

Epithelium

Subepithelial layer

there are technical considerations to ensure consistency in methodologies and data analysis. Control of gastrointestinal function Secretion, absorption, motor activity, growth and differentiation of the gut are all modulated by a combination of neuronal and hormonal factors. The nervous system and gastrointestinal function The central nervous system (CNS), the autonomic system (ANS) and the enteric nervous system (ENS) interact to regulate gut function. The ANS comprises: • parasympathetic pathways (vagal and sacral efferent), which are cholinergic, and increase smooth muscle tone and promote sphincter relaxation • sympathetic pathways, which release noradrenaline (norepinephrine), reduce smooth muscle tone and stimulate sphincter contraction. The enteric nervous system In conjunction with the ANS, the ENS senses gut contents and conditions, and regulates motility, fluid exchange, secretion, blood flow and other key gut functions. It comprises two major networks intrinsic to the gut wall. The myenteric (Auerbach's) plexus in the smooth muscle layer regulates motor control; and the submucosal (Meissner's) plexus exerts secretory control over the epithelium, entero-endocrine cells and submucosal vessels. Together, these plexuses form a two-layered neuronal mesh along the length of Intestinal microbiota The human microbiota comprises 1014 microbial residents in the human body, vastly outnumbering host cells. Indeed, the number of bacterial genes in the microbiota genome exceeds that of the host by 100-fold or more. This represents a vast ecosystem that is central to health and homeostasis, and is disordered in disease. In terms of nomenclature, 'microbiota' refers to the microorganisms that live in a particular niche, while 'microbiome' refers to the collective genomes of these microbiota. The metabolic capacity of the gut microbiota is equivalent to that of the liver. The Human Microbiome Project revealed that there are unique communities at different body sites and in the gut particular phyla predominate: namely, Firmicutes, Bacteriodetes, Proteobacteria and Actinobacteria. There is a degree of heritability of this microbiota, as shown in twin studies, but it is clear that there are many environmental factors that can impact, including diet, drugs, physical activity, smoking, stress and natural ageing. Generally, we acquire our adult intestinal microbiota by the age of 2 years. A dysbiosis or imbalance between the different components of the intestinal microbiota has been associated with diseases of the gastrointestinal tract, such as inflammatory bowel disease and colorectal cancer; liver disease, including hepatocellular carcinoma; and pathologies outside the gastrointestinal tract, such as diabetes, obesity, cardiovascular disorders, cerebrovascular disorders, asthma and psychiatric disorders, such as depression. Many challenges remain in understanding the intestinal microbiota and how it impacts on health and disease. It is not clear what constitutes a 'healthy' phenotype; there are questions over best sampling practice from either the faecal stream or the mucosa; and Fig. 21.10 The normal colon, rectum and anal canal. Superior mesenteric artery Caecum Appendix Inferior mesenteric artery Rectum Anal canal External anal sphincter Internal anal sphincter Sigmoid colon Descending colon Ascending colon Ileocaecal valve Transverse colon

 Gut hormones The origin, action and control of the major gut hormones, peptides and non-peptide signalling transmitters are summarised in Box 21.2. Investigation of gastrointestinal disease A wide range of tests is available for the investigation of patients with gastrointestinal symptoms. These can be classified broadly into tests of structure, tests for infection and tests of function. Imaging Plain X-rays Plain X-rays of the abdomen are useful

in the diagnosis of intestinal obstruction or paralytic ileus, where dilated loops of bowel and (in the erect position) fluid levels may be seen (Fig. 21.11). Calcified lymph nodes, gallstones and renal stones can also be detected. Chest X-ray (performed with the patient in erect position) is useful in the diagnosis of suspected perforation, as it shows subdiaphragmatic free air (Fig. 21.11). the gut. Although connected centrally via the ANS, the ENS can function autonomously using a variety of transmitters, including acetylcholine, noradrenaline (norepinephrine), 5-HT, nitric oxide, substance P and calcitonin gene-related peptide (CGRP). There are local reflex loops within the ENS but also loops involving the coeliac and mesenteric ganglia and the paravertebral ganglia. The parasympathetic system generally stimulates motility and secretion, while the sympathetic system generally acts in an inhibitory manner. Peristalsis Peristalsis is a reflex triggered by gut wall distension, which consists of a wave of circular muscle contraction to propel contents from the oesophagus to the rectum. It can be influenced by innervation but functions independently. It results from a basic electrical rhythm originating from the interstitial cells of Cajal in the circular layer of intestinal smooth muscle. These are stellate cells of mesenchymal origin with smooth muscle features, which act as the ‘pacemaker’ of the gut. Migrating motor complexes Migrating motor complexes (MMCs) are waves of contraction spreading from the stomach to the ileum, occurring at a frequency of about 5 per minute every 90 minutes or so, between meals and during fasting. They may serve to sweep intestinal contents distally in preparation for the next meal and are inhibited by eating. 21.2 Gut hormones and peptides Hormone Origin Stimulus Action Gastrin Stomach (G cell) Products of protein digestion Suppressed by acid and somatostatin Stimulates gastric acid secretion Stimulates growth of gastrointestinal mucosa Somatostatin Throughout gastrointestinal tract (D cell) Fat ingestion Inhibits gastrin and insulin secretion Decreases acid secretion Decreases absorption Inhibits pancreatic secretion Cholecystokinin (CCK) Duodenum and jejunum (I cells); also ileal and colonic nerve endings Products of protein digestion Fat and fatty acids Suppressed by trypsin Stimulates pancreatic enzyme secretion Stimulates gallbladder contraction Relaxes sphincter of Oddi Modulates satiety Decreases gastric acid secretion Reduces gastric emptying Regulates pancreatic growth Secretin Duodenum and jejunum (S cells) Duodenal acid Fatty acids Stimulates pancreatic fluid and bicarbonate secretion Decreases acid secretion Reduces gastric emptying Motilin Duodenum, small intestine and colon (Mo cells) Fasting Dietary fat Regulates peristaltic activity, including migrating motor complexes (MMCs) Gastric inhibitory polypeptide (GIP) Duodenum (K cells) and jejunum Glucose and fat Stimulates insulin release (also known as glucose-dependent insulinotrophic polypeptide) Inhibits acid secretion Enhances satiety Glucagon-like peptide-1 (GLP-1) Ileum and colon (L cells) Carbohydrates, protein and fat Stimulates insulin release Inhibits acid secretion and gastric emptying Enhances satiety Vasoactive intestinal peptide (VIP) Nerve fibres throughout gastrointestinal tract Unknown Has vasodilator action Relaxes smooth muscle Stimulates water and electrolyte secretion Ghrelin Stomach Fasting Inhibited by eating Stimulates appetite, acid secretion and gastric emptying Peptide YY Ileum and colon Feeding Modulates satiety

The double contrast technique improves mucosal visualisation by using gas to distend the barium-coated intestinal surface. Contrast studies are useful for detecting filling defects, such as tumours, strictures, ulcers and motility disorders, but are inferior to endoscopic procedures and more sophisticated cross-sectional imaging techniques, such as computed tomography and magnetic resonance imaging. The major uses and limitations of various contrast studies are shown in Box

21.3 and Figure 21.12. Contrast studies X-rays with contrast medium are usually performed to assess not only anatomical abnormalities but also motility. Barium sulphate provides good mucosal coating and excellent opacification but can precipitate impaction proximal to an obstructive lesion. Water-soluble contrast is used to opacify bowel prior to abdominal computed tomography and in cases of suspected perforation. Fig. 21.11 Examples of plain X-rays. A Abdominal X-ray showing dilatation of loops of small bowel (arrows), which are indicative of obstruction (in this case due to adhesions from previous surgery). B Chest X-ray showing free air under both hemi-diaphragms (arrows), which is indicative of acute perforation of an abdominal viscus. A B 21.3 Contrast radiology in the investigation of gastrointestinal disease Barium swallow/meal Barium follow-through Barium enema Indications and major uses Motility disorders (achalasia and gastroparesis) Perforation or fistula (non-ionic contrast) Diarrhoea and abdominal pain of small bowel origin Possible obstruction by strictures Suspected malabsorption Assessment of Crohn's disease Altered bowel habit Evaluation of strictures or diverticular disease Megacolon Chronic constipation Limitations Risk of aspiration Poor mucosal detail Low sensitivity for early cancer Inability to biopsy Time-consuming nature Radiation exposure Relative insensitivity Difficulty in frail or incontinent patients Sigmoidoscopy needed to see rectum Low sensitivity for lesions < 1 cm Fig. 21.12 Examples of contrast radiology. A Barium swallow showing a large pharyngeal pouch (P) with retained contrast creating an air–fluid level. B Barium follow-through. There are multiple diverticula (arrows) in this patient with jejunal diverticulosis. C Barium enema showing severe diverticular disease. There is tortuosity and narrowing of the sigmoid colon with multiple diverticula (arrows). A P B C

774 • GASTROENTEROLOGY 21.4 Imaging in gastroenterology Ultrasound Computed tomography (CT) Magnetic resonance imaging (MRI) CT–positron emission tomography (CT-PET) Indications and major uses Abdominal masses Organomegaly Ascites Biliary tract dilatation Gallstones Guided biopsy of lesions Small bowel imaging Assessment of pancreatic disease Hepatic tumour deposits CT colonography ('virtual colonoscopy') Tumour staging Assessment of lesion vascularity Abscesses and collections Hepatic tumour staging MRCP Pelvic/perianal disease Crohn's fistulae Small bowel visualisation Detection of metastases not seen on ultrasound or CT Images can be fused with CT to form composite image Limitations Low sensitivity for small lesions Little functional information Operator-dependent Gas and obesity may obscure view Cost Radiation dose Claustrophobic patients Contraindicated in presence of metallic prostheses, cardiac pacemaker, cochlear implants Signal detection depends on metabolic activity within tumour – not all are metabolically active Fig. 21.13 Examples of ultrasound, CT and MRI. A Ultrasound showing large gallstone (arrow) with acoustic shadowing. B Multidetector coronal CT showing large solid and cystic malignant tumour in the pancreatic tail (arrow). (PV = portal vein; L = liver) C Pelvic MRI showing large pelvic abscess (arrow) posterior to the rectum in a patient with Crohn's disease. D Fused CT-PET image showing two liver metastases (arrows). A B C D L PV Ultrasound, computed tomography and magnetic resonance imaging Ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI) are key tests in the evaluation of intra-abdominal disease. They are non-invasive and offer detailed images of the abdominal contents.
Fluorodeoxyglucose–positron emission tomography (FDG-PET) is increasingly used in the staging of malignancies and images may be fused with CT to enhance localisation. Their main applications are summarised in Box 21.4 and Figure 21.13. Endoscopy Videoendoscopes provide high-definition imaging and accessories can be passed down the endoscope to allow both diagnostic and therapeutic procedures, some of which are illustrated in Figure 21.14. Endoscopes with magnifying

lenses allow almost microscopic detail to be observed, and imaging modalities, such as confocal endomicroscopy, autofluorescence and ‘narrow-band imaging’, are increasingly used to detect subtle abnormalities not visible by standard ‘white light’ endoscopy. Upper gastrointestinal endoscopy This is performed under light intravenous benzodiazepine sedation, or using only local anaesthetic throat spray after the patient has fasted for at least 4 hours. With the patient in the left lateral position, the entire oesophagus (excluding pharynx), stomach and first two parts of duodenum can be seen. Indications, contraindications and complications are given in Box 21.5. Endoscopic ultrasound Endoscopic ultrasound (EUS) combines endoscopy with intraluminal ultrasonography using a high-frequency transducer to produce high-resolution ultrasound images. This allows visualisation through the wall of the gastrointestinal tract and into surrounding tissues, e.g. the pancreas or lymph nodes. It can therefore be used to perform fine needle aspiration or biopsy of mass lesions. EUS is helpful in the diagnosis of pancreatic tumours, chronic pancreatitis, pancreatic cysts, cholangiocarcinoma, common bile duct stones, ampullary lesions and submucosal tumours. It also plays an important role in the staging of certain cancers, e.g. those of oesophagus and pancreas. EUS can also be therapeutic, as in drainage of pancreatic fluid collections and coeliac plexus block for pain management. Possible complications of EUS include bleeding, infection, cardiopulmonary events and perforation. Capsule endoscopy Capsule endoscopy (Fig. 21.15) uses a capsule containing an imaging device, battery, transmitter and antenna; as it traverses the small intestine, it transmits images to a batterypowered recorder worn on a belt round the patient’s waist. After approximately 8 hours, the capsule is excreted. Images from the capsule are analysed as a video sequence and it is usually possible to localise the segment of small bowel in which lesions are seen. Abnormalities detected usually require enteroscopy

Fig. 21.14 Examples of therapeutic techniques in endoscopy. Control of bleeding Injection sclerotherapy Diathermy Variceal ligation Laser therapy Treatment of tumours Laser therapy Polypectomy Photodynamic therapy/radiofrequency ablation Treatment of strictures Stent insertion Balloon dilatation Bouginage Management of biliary and pancreatic disease Basket retrieval Endoscopic clipping Endoscopic mucosal resection Endoscopic submucosal dissection (ESD) Stent insertion Pseudocyst drainage Sphincterotomy Fig. 21.15 Wireless capsule endoscopy. A Examples of capsules. B Capsule endoscopy image of bleeding jejunal vascular malformation. A, Courtesy of Given Imaging. A B Indications • Dyspepsia in patients > 55 years of age or with alarm symptoms • Atypical chest pain • Dysphagia • Vomiting • Weight loss • Acute or chronic gastrointestinal bleeding • Screening for oesophageal varices in chronic liver disease • Abnormal CT scan or barium meal • Duodenal biopsies in the investigation of malabsorption and confirmation of a diagnosis of coeliac disease prior to commencement of gluten-free diet • Therapy, including treatment of bleeding lesions, banding/injection of varices, dilatation of strictures, insertion of stents, placement of percutaneous gastrostomies, ablation of Barrett’s oesophagus and resection of high-grade dysplastic lesions and early neoplasia in the upper gastrointestinal tract Contraindications • Severe shock • Recent myocardial infarction, unstable angina, cardiac arrhythmia* • Severe respiratory disease* • Atlantoaxial subluxation* • Possible visceral perforation Complications • Cardiorespiratory depression due to sedation • Aspiration pneumonia • Perforation *These are ‘relative’ contraindications; in experienced hands, endoscopy can be safely performed. 21.5 Upper gastrointestinal endoscopy

776 • GASTROENTEROLOGY 21.6 Wireless capsule endoscopy Indications • Obscure gastrointestinal bleeding • Small bowel Crohn’s disease • Assessment of coeliac disease and its complications • Screening and surveillance in familial polyposis syndromes Contraindications • Known or suspected small bowel stricture (risk of capsule retention) • Caution in people with pacemakers or implantable defibrillators Complications • Capsule retention (< 1%) for confirmation and therapy. Indications, contraindications and complications are listed in Box 21.6. Double balloon enteroscopy While endoscopy can reach the proximal small intestine in most patients, a technique called double balloon enteroscopy is also available, which uses a long endoscope with a flexible overtube. Sequential and repeated inflation and deflation of balloons on the tip of the overtube and enteroscope allow the operator to push and pull along the entire length of the small intestine to the terminal ileum, in order to diagnose or treat small bowel lesions detected by capsule endoscopy or other imaging modalities. Indications, contraindications and complications are listed in Box 21.7. Sigmoidoscopy and colonoscopy Sigmoidoscopy can be carried out either in the outpatient clinic using a 20 cm rigid plastic sigmoidoscope or in the endoscopy suite using a 60 cm flexible colonoscope following bowel preparation. When sigmoidoscopy is combined with proctoscopy, accurate detection of haemorrhoids, ulcerative colitis and distal colorectal neoplasia is possible. After full bowel cleansing, it is possible to examine the entire colon and the terminal ileum using a longer colonoscope. Indications, contraindications and complications of colonoscopy are listed in Box 21.8. 21.7 Double balloon enteroscopy Indications Diagnostic • Obscure gastrointestinal bleeding • Malabsorption or unexplained diarrhoea • Suspicious radiological findings • Suspected small bowel tumour • Surveillance of polyposis syndromes Therapeutic • Coagulation/diathermy of bleeding lesions • Jejunostomy placement Contraindications • As for upper gastrointestinal endoscopy Complications • As for upper gastrointestinal endoscopy • Post-procedure abdominal pain (≤ 20%) • Pancreatitis (1–3%) • Perforation (especially after resection of large polyps) 21.9 Endoscopy in old age • Tolerance: endoscopic procedures are generally well tolerated, even in very old people. • Side-effects from sedation: older people are more sensitive, and respiratory depression, hypotension and prolonged recovery times are more common. • Bowel preparation for colonoscopy: can be difficult in frail, immobile people. Sodium phosphate-based preparations can cause dehydration or hypotension and should be avoided in those with underlying cardiac or renal failure. Minimal-preparation CT colonograms provide an excellent alternative in these individuals. • Antiperistaltic agents: hyoscine should be avoided in those with glaucoma and can also cause tachyarrhythmias. Glucagon is preferred if an antiperistaltic agent is needed. Magnetic resonance cholangiopancreatography Magnetic resonance cholangiopancreatography (MRCP) has largely replaced endoscopic retrograde cholangiopancreatography (ERCP) in the evaluation of obstructive jaundice since it produces comparable images of the biliary tree and pancreas, providing information that complements that obtained from CT and endoscopic ultrasound examination (EUS). Endoscopic retrograde cholangiopancreatography Using a side-viewing duodenoscope, it is possible to cannulate the main pancreatic duct and common bile duct. Nowadays, ERCP is used mainly in the treatment of a range of biliary and pancreatic diseases that have been identified by other imaging techniques such as MRCP, EUS and CT. Indications for and risks of ERCP are listed in Box 21.10. Histology Biopsy material obtained endoscopically or percutaneously can provide useful information (Box 21.11). 21.8 Colonoscopy Indications* • Suspected inflammatory bowel disease • Chronic diarrhoea • Altered bowel habit • Rectal bleeding or iron deficiency anaemia • Assessment of abnormal CT colonogram or barium enema • Colorectal cancer screening • Colorectal adenoma and carcinoma follow-up • Therapeutic procedures, including endoscopic resection, dilatation of strictures, laser, stent insertion and argon plasma coagulation Contraindications • Acute severe

ulcerative colitis (unprepared flexible sigmoidoscopy is preferred) • As for upper gastrointestinal endoscopy Complications • Cardiorespiratory depression due to sedation • Perforation • Bleeding following polypectomy *Colonoscopy is not useful in the investigation of constipation.

Tests of infection Bacterial cultures Stool cultures are essential in the investigation of diarrhoea, especially when it is acute or bloody, in order to identify pathogenic organisms (Ch. 11). Serology Detection of antibodies plays a limited role in the diagnosis of gastrointestinal infection caused by organisms such as Helicobacter pylori, Salmonella species and Entamoeba histolytica. Breath tests Non-invasive breath tests for H. pylori infection are discussed on page 800 and breath tests for suspected small intestinal bacterial overgrowth on page 808. Tests of function A number of dynamic tests can be used to investigate aspects of gut function, including digestion, absorption, inflammation and epithelial permeability. Some of the more common ones are listed in Box 21.12. In the assessment of suspected malabsorption, blood tests (full blood count, erythrocyte sedimentation rate (ESR), and measurement of C-reactive protein (CRP), folate, vitamin B12, *Laparoscopic surgery is preferred in fit individuals who also require cholecystectomy. 21.10 Endoscopic retrograde cholangiopancreatography Indications Diagnostic • Biliary or pancreatic disease where other imaging is equivocal or contraindicated • Ampullary biopsy or biliary cytology Therapeutic • Biliary disease: Removal of common bile duct calculi* Palliation of malignant biliary obstruction Management of biliary leaks/damage complicating surgery Dilatation of benign strictures Primary sclerosing cholangitis • Pancreatic disease: Drainage of pancreatic pseudocysts and fistulae Removal of pancreatic calculi (selected cases) Contraindications • Severe cardiopulmonary comorbidity • Coagulopathy Complications • Occur in 5–10% with a 30-day mortality of 0.5–1% General • As for upper endoscopy Specific • Biliary disease: Bleeding following sphincterotomy Cholangitis (if biliary obstruction is not relieved by ERCP) Gallstone impaction • Pancreatic disease: Acute pancreatitis Infection of pseudocyst 21.11 Reasons for biopsy or cytological examination • Suspected malignant lesions • Assessment of mucosal abnormalities • Diagnosis of infection (Candida, Helicobacter pylori, Giardia lamblia) • Analysis of genetic mutations 21.12 Tests of gastrointestinal function Process Test Principle Comments Absorption Lactose Lactose H2 breath test Measurement of breath H2 content after 50 g oral lactose. Undigested sugar is metabolised by colonic bacteria in hypolactasia and expired hydrogen is measured Non-invasive and accurate. May provoke pain and diarrhoea in sufferers Bile acids 75SeHCAT test Isotopic quantification of 7-day whole-body retention of oral dose 75Se-labelled homocholyltaurine (> 15% = normal, 5–15% borderline, < 5% = abnormal) Accurate and specific but requires two visits and involves radiation. Results can be equivocal. Serum 7α-hydroxycholestenone is almost as sensitive and specific Serum 7α-hydroxycholestenone Intermediate metabolite of the bile acid synthetic pathway. Serum levels indicate activity of the pathway and are elevated in bile acid diarrhoea Simple test to perform and only marginally less sensitive and specific than 75SeHCAT test Pancreatic exocrine function Pancreolauryl test Pancreatic esterases cleave fluorescein dilaurate after oral ingestion. Fluorescein is absorbed and quantified in urine Accurate and avoids duodenal intubation Takes 2 days. Accurate urine collection essential. Rarely performed Faecal elastase Immunoassay of pancreatic enzymes on stool sample Simple, quick and avoids urine collection. Does not detect mild disease Mucosal inflammation/ permeability Faecal calprotectin A protein secreted non-specifically by neutrophils into the colon in response to inflammation or neoplasia Useful screening test for gastrointestinal inflammation and

for monitoring patients with Crohn’s disease and ulcerative colitis. Poor sensitivity for cancer (75SeHCAT = 75Se-homocholic acid taurine)

778 • GASTROENTEROLOGY iron status, albumin, calcium and phosphate) are essential, and endoscopy is undertaken to obtain mucosal biopsies. Faecal calprotectin is very sensitive at detecting mucosal inflammation. Oesophageal motility A barium swallow can give useful information about oesophageal motility. Videofluoroscopy, with joint assessment by a speech and language therapist and a radiologist, may be necessary in difficult cases. Oesophageal manometry (see Fig. 21.1), often in conjunction with 24-hour pH measurements, is of value in diagnosing cases of refractory gastro-oesophageal reflux, achalasia and non-cardiac chest pain. Oesophageal impedance testing is useful for detecting non-acid or gas reflux events, especially in patients with atypical symptoms or those who respond poorly to acid suppression. Gastric emptying This involves administering a test meal containing solids and liquids labelled with different radioisotopes and measuring the amount retained in the stomach afterwards (Box 21.13). It is useful in the investigation of suspected delayed gastric emptying (gastroparesis) when other studies are normal. Colonic and anorectal motility A plain abdominal X-ray taken on day 5 after ingestion of differentshaped inert plastic pellets on days 1–3 gives an estimate of whole-gut transit time. The test is useful in the evaluation of chronic constipation, when the position of any retained pellets can be observed, and helps to differentiate cases of slow transit from those due to obstructed defecation. The mechanism of defecation and anorectal function can be assessed by anorectal manometry, electrophysiological tests and defecating proctography. Radioisotope tests Many different radioisotope tests are used (Box 21.13). In some, structural information is obtained, such as the localisation of a Meckel’s diverticulum. Others provide functional information, such as the rate of gastric emptying or ability to reabsorb bile acids. Yet others are tests of infection and rely on the presence of bacteria to hydrolyse a radio-labelled test substance followed by detection of the radioisotope in expired air, such as the urea breath test for H. pylori. 21.13 Commonly used radioisotope tests in gastroenterology Test Isotope Major uses and principle of test Gastric emptying study 99mTc-sulphur 111In-DTPA Assessment of gastric emptying, particularly for possible gastroparesis Urea breath test 13C-urea Non-invasive diagnosis of Helicobacter pylori. Bacterial urease enzyme splits urea to ammonia and CO2, which is detected in expired air Meckel’s scan 99mTc-pertechnate Diagnosis of Meckel’s diverticulum in cases of obscure gastrointestinal bleeding. Isotope is injected intravenously and localises in ectopic parietal mucosa within diverticulum Somatostatin receptor scintigraphy (SRS) 111In-DTPA-octreotide Labelled somatostatin analogue binds to cell surface somatostatin receptors on pancreatic neuro-endocrine tumours Positron emission tomography (PET) 18F-fluorodeoxyglucose (FDG) 68Gallium-labelled somatostatin analogue Staging high-grade cancers More sensitive and specific than SRS for staging neuro-endocrine tumours Gut hormone testing Excess gut hormone secretion by some gastrointestinal and pancreatic neuro-endocrine tumours can be assessed by measuring levels in blood. Commonly measured hormones include gastrin, somatostatin, vasoactive intestinal polypeptide (VIP) and pancreatic polypeptide. Presenting problems in gastrointestinal disease Dysphagia Dysphagia is defined as difficulty in swallowing. It may coexist with heartburn or vomiting but should be distinguished from both globus sensation (in which anxious people feel a lump in the throat without organic cause) and odynophagia (pain during swallowing, usually from gastro-oesophageal reflux or candidiasis). Dysphagia can occur due to problems in the oropharynx or oesophagus (Fig. 21.16). Oropharyngeal disorders affect the initiation of swallowing at the pharynx and upper oesophageal sphincter. The patient has difficulty initiating swallowing and

complains of choking, nasal regurgitation or tracheal aspiration. Drooling, dysarthria, hoarseness and cranial nerve or other neurological signs may be present. Oesophageal disorders cause dysphagia by obstructing the lumen or by affecting motility. Patients with oesophageal disease complain of food ‘sticking’ after swallowing, although the level at which this is felt correlates poorly with the true site of obstruction. Swallowing of liquids is normal until strictures become extreme. Investigations Dysphagia should always be investigated urgently. Endoscopy is the investigation of choice because it allows biopsy and dilatation of strictures. Even if the appearances are normal, biopsies should be taken to look for eosinophilic oesophagitis. If no abnormality is found, then barium swallow with videofluoroscopic swallowing assessment is indicated to detect major motility disorders. In some cases, oesophageal manometry is required. High-resolution manometry allows accurate classification of abnormalities. Figure 21.16 summarises a diagnostic approach to dysphagia and lists the major causes.

‘alarm’ features requiring urgent investigation (Box 21.15) and to detect atypical symptoms that might be due to problems outside the gastrointestinal tract. Dyspepsia affects up to 80% of the population at some time in life and most patients have no serious underlying disease. People who present with new dyspepsia at an age of more than 55 years and younger patients unresponsive to empirical treatment require investigation to exclude serious disease. An algorithm for the investigation of dyspepsia is outlined in Figure 21.17. Heartburn and regurgitation Heartburn describes retrosternal, burning discomfort, often rising up into the chest and sometimes accompanied by regurgitation of acidic or bitter fluid into the throat. These symptoms often occur after meals, on lying down or with bending, straining or heavy lifting. They are classical symptoms of gastro-oesophageal reflux but up to 50% of patients present with other symptoms, such as chest pain, belching, halitosis, chronic cough or sore throats. In young patients with typical symptoms and a good response to dietary changes, antacids or acid suppression investigation is not required, but in patients over 55 years of age and those with alarm symptoms or atypical features urgent endoscopy is necessary. Dyspepsia Dyspepsia describes symptoms such as discomfort, bloating and nausea, which are thought to originate from the upper gastrointestinal tract. There are many causes (Box 21.14), including some arising outside the digestive system. Heartburn and other ‘reflux’ symptoms are separate entities and are considered elsewhere. Although symptoms often correlate poorly with the underlying diagnosis, a careful history is important to detect Fig. 21.16 Investigation of dysphagia. Benign Malignant Oesophagitis Dysmotility Stricture Manometry/ barium swallow Endoscopy and biopsy Oesophageal dysphagia Videofluoroscopic swallowing assessment and neurological investigation Oropharyngeal dysphagia Food 'sticking' after swallowing ± regurgitation Dysphagia Neurological disease • Bulbar palsy • Pseudobulbar palsy • Myasthenia gravis • Achalasia • Non-specific motility disorder • Peptic • Candidiasis • Eosinophilic • Peptic • Fibrous rings • Eosinophilic oesophagitis • Drugs, e.g. bisphosphonates • Carcinoma of the oesophagus • Carcinoma of the stomach • Extrinsic compression Difficulty initiating swallow ± choking or aspiration 21.14 Causes of dyspepsia Upper gastrointestinal disorders • Peptic ulcer disease • Acute gastritis • Gallstones • Oesophageal spasm • Non-ulcer dyspepsia • Irritable bowel syndrome Other gastrointestinal disorders • Pancreatic disease (cancer, chronic pancreatitis) • Colonic carcinoma • Hepatic disease (hepatitis, metastases) Systemic disease • Renal failure • Hypercalcaemia Drugs • Non-steroidal antiinflammatory drugs (NSAIDs) • Glucocorticoids • Iron and potassium supplements • Digoxin Others • Psychological (anxiety, depression) • Alcohol 21.15

Alarm features in dyspepsia • Weight loss • Anaemia • Vomiting • Haematemesis and/or melaena • Dysphagia • Palpable abdominal mass

780 • GASTROENTEROLOGY Fig. 21.17 Investigation of dyspepsia. < 55 years Urgent endoscopy

> 55 years Test for Helicobacter pylori, e.g. serology, stool antigen or 13C urea breath test Endoscopy Positive Negative Helicobacter pylori eradication Treat symptomatically or consider other diagnoses Symptoms resolve Symptoms persist No follow-up Endoscopy Dyspepsia Are there 'alarm' features? Yes No Fig. 21.18 Causes of vomiting. (NSAIDs = non-steroidal anti-inflammatory drugs) Alcoholism Central nervous system disorders • Vestibular neuronitis • Migraine • Raised intracranial pressure • Meningitis Gastroduodenal • Peptic ulcer disease • Gastric cancer • Gastroparesis The acute abdomen • Appendicitis • Cholecystitis • Pancreatitis • Intestinal obstruction Metabolic • Diabetic ketoacidosis • Addison’s disease Uraemia Infections • Hepatitis • Gastroenteritis • Urinary tract infection Drugs • NSAIDs • Opiates • Digoxin • Antibiotics • Cytotoxins Psychogenic pressure and, combined with relaxation of the lower oesophageal sphincter, results in forcible ejection of gastric contents. It is important to distinguish true vomiting from regurgitation and to elicit whether the vomiting is acute or chronic (recurrent), as the underlying causes may differ. The major causes are shown in Figure 21.18. Gastrointestinal bleeding Acute upper gastrointestinal haemorrhage This is the most common gastrointestinal emergency, accounting for 50–170 admissions to hospital per 100 000 of the population each year in the UK. The mortality of patients admitted to hospital is about 10% but there is some evidence that outcome is better when individuals are treated in specialised units. Risk scoring systems have been developed to stratify the risk of needing endoscopic therapy or of having a poor outcome (Box 21.16). The advantage of the Blatchford score is that it may be used before endoscopy to predict the need for intervention to treat bleeding. Low scores (2 or less) are associated with a very low risk of adverse outcome. The common causes are shown in Figure 21.19. Clinical assessment Haematemesis is red with clots when bleeding is rapid and profuse, or black (‘coffee grounds’) when less severe. Syncope may occur and is caused by hypotension from intravascular volume depletion. Symptoms of anaemia suggest chronic bleeding. Melaena is the passage of black, tarry stools containing altered blood; it is usually caused by bleeding from the upper gastrointestinal tract, although haemorrhage from the right side of the colon is occasionally responsible. The characteristic colour and smell are the result of the action of digestive enzymes and of bacteria on haemoglobin. Severe acute upper gastrointestinal bleeding can sometimes cause maroon or bright red stool. Vomiting Vomiting is a complex reflex involving both autonomic and somatic neural pathways. Synchronous contraction of the diaphragm, intercostal muscles and abdominal muscles raises intra-abdominal

1. Intravenous access The first step is to gain intravenous access using at least one large-bore cannula.
2. Initial clinical assessment • Define circulatory status. Severe bleeding causes tachycardia, hypotension and oliguria. The patient is cold and sweating, and may be agitated. • Seek evidence of liver disease (p. 846). Jaundice, cutaneous stigmata, hepatosplenomegaly and ascites may be present in decompensated cirrhosis. • Identify comorbidity. The presence of cardiorespiratory, cerebrovascular or renal disease is important, both because these may be worsened by acute bleeding and because they increase the hazards of endoscopy and surgical operations. These factors can be combined using the Blatchford score (Box 21.16), which can be calculated at the bedside. A score of 2 or less is associated with a good prognosis, while progressively higher scores are associated with poorer outcomes.
3. Basic investigations • Full blood count. Chronic or subacute bleeding leads to anaemia but the haemoglobin concentration may be normal after sudden, major bleeding until haemodilution occurs. Thrombocytopenia may be a clue to the presence of hypersplenism in chronic liver disease. • Urea and electrolytes. This test may show evidence of renal failure. The blood urea rises as the absorbed products of luminal blood are metabolised by the liver; an elevated blood urea with normal creatinine concentration implies severe bleeding. • Liver function tests. These may show evidence of chronic liver disease. • Prothrombin time. Check when there is a clinical suggestion of liver disease or patients are anticoagulated. • Cross-matching. At least 2 units of blood should be cross-matched if a significant bleed is suspected. 21.16 Modified Blatchford score: risk stratification in acute upper gastrointestinal bleeding Admission risk marker Score component value Blood urea ≥ 25 mmol/L (70 mg/dL)

10–25 mmol/L (28–70 mg/dL)

8–10 mmol/L (21.4–28 mg/dL)

6.5–8 mmol/L (18.2–22.4 mg/dL)

< 6.5 mmol/L (18.2 mg/dL)

Haemoglobin for men < 100 g/L (10 g/dL)

100–119 g/L (10–11.9 g/dL)

120–129 g/L (12–12.9 g/dL)

≥ 130 g/L (13 g/dL)

Haemoglobin for women < 100 g/L (10 g/dL)

100–119 g/L (10–11.9 g/dL)

≥ 120 g/L (12 g/dL)

Systolic blood pressure < 90 mmHg

90–99 mmHg

100–109 mmHg

> 109 mmHg

Other markers Presentation with syncope

Hepatic disease

Cardiac failure

Pulse ≥ 100 beats/min

Presentation with melaena

None of the above

Fig. 21.19 Causes of acute upper gastrointestinal haemorrhage. Frequency is given in parentheses. (NSAIDs = non-steroidal anti-inflammatory drugs) Liver disease Portal vein thrombosis Varices (2 – 9%) Oesophagitis (10%) Usually with hiatus hernia Retching Mallory–Weiss tear (5%) Cancer of stomach or oesophagus (2%) NSAIDs Helicobacter pylori Peptic ulcer (35 – 50%) Vascular malformations (5%) Aortic graft Aorto-duodenal fistula (0.2%) NSAIDs Alcohol Gastric erosions (10 – 20%) Management The principles of emergency management of non-variceal bleeding are discussed in detail below. Management of variceal bleeding is discussed on page 869.

782 • GASTROENTEROLOGY can also be carried out (a biopsy must be taken to exclude carcinoma). Local excision may be performed, but when neither is possible, partial gastrectomy is required. 9. Eradication Following treatment for ulcer bleeding, all patients should avoid non-steroidal anti-inflammatory drugs (NSAIDs) and those who test positive for H. pylori infection should receive eradication therapy (p. 800). Successful eradication should be confirmed by urea breath or faecal antigen testing. Lower gastrointestinal bleeding This may be caused by haemorrhage from the colon, anal canal or small bowel. It is useful to distinguish those patients who present with profuse, acute bleeding from those who present with chronic or subacute bleeding of lesser severity (Box 21.17). Severe acute lower gastrointestinal bleeding This presents with profuse red or maroon diarrhoea and with shock. Diverticular disease is the most common cause and is often due to erosion of an artery within the mouth of a diverticulum. Bleeding almost always stops spontaneously, but if it does not, the diseased segment of colon should be resected after confirmation of the site by angiography or colonoscopy. Angiodysplasia is a disease of the elderly, in which vascular malformations develop in the proximal colon. Bleeding can be acute and profuse; it usually 4. Resuscitation Intravenous crystalloid fluids should be given to raise the blood pressure, and blood should be transfused when the patient is actively bleeding with low blood pressure and tachycardia. Comorbidities should be managed as appropriate. Patients with

suspected chronic liver disease should receive broad-spectrum antibiotics. 5. Oxygen This should be given to all patients in shock. 6. Endoscopy This should be carried out after adequate resuscitation, ideally within 24 hours, and will yield a diagnosis in 80% of cases. Patients who are found to have major endoscopic stigmata of recent haemorrhage (Fig. 21.20) can be treated endoscopically using a thermal or mechanical modality, such as a ‘heater probe’ or endoscopic clips, combined with injection of dilute adrenaline (epinephrine) into the bleeding point (‘dual therapy’). A biologically inert haemostatic mineral powder (TC325, ‘haemospray’) can be used as rescue therapy when standard therapy fails. This may stop active bleeding and, combined with intravenous proton pump inhibitor (PPI) therapy, may prevent rebleeding, thus avoiding the need for surgery. Patients found to have bled from varices should be treated by band ligation (p. 870); if this fails, balloon tamponade is another option, while arrangements are made for a transjugular intrahepatic portosystemic shunt (TIPSS). 7. Monitoring Patients should be closely observed, with hourly measurements of pulse, blood pressure and urine output. 8. Surgery Surgery is indicated when endoscopic haemostasis fails to stop active bleeding and if rebleeding occurs on one occasion in an elderly or frail patient, or twice in a younger, fitter patient. If available, angiographic embolisation is an effective alternative to surgery in frail patients. The choice of operation depends on the site and diagnosis of the bleeding lesion. Duodenal ulcers are treated by under-running, with or without pyloroplasty. Under-running for gastric ulcers Fig. 21.20 Major stigmata of recent haemorrhage and endoscopic treatment. A Active bleeding from a duodenal ulcer. B Haemostasis is achieved after endoscopic injection of adrenaline (epinephrine) and application of a heater probe. A B 21.17 Causes of lower gastrointestinal bleeding Severe acute • Diverticular disease • Angiodysplasia • Ischaemia • Meckel’s diverticulum • Inflammatory bowel disease (rarely) Moderate, chronic/subacute • Fissure • Haemorrhoids • Inflammatory bowel disease • Carcinoma • Large polyps • Angiodysplasia • Radiation enteritis • Solitary rectal ulcer

used to define a source of bleeding prior to enteroscopy. When all else fails, laparotomy with on-table endoscopy is indicated. Chronic occult gastrointestinal bleeding In this context, occult means that blood or its breakdown products are present in the stool but cannot be seen by the naked eye. Occult bleeding may reach 200 mL per day and cause iron deficiency anaemia. Any cause of gastrointestinal bleeding may be responsible but the most important is colorectal cancer, particularly carcinoma of the caecum, which may produce no gastrointestinal symptoms. In clinical practice, investigation of the upper and lower gastrointestinal tract should be considered whenever a patient presents with unexplained iron deficiency anaemia. Testing the stool for the presence of blood is unnecessary and should not influence whether or not the gastrointestinal tract is imaged because bleeding from tumours is often intermittent and a negative faecal occult blood (FOB) test does not exclude the diagnosis. The only value of FOB testing is as a means of population screening for colonic neoplasia in asymptomatic individuals (p. 832). Diarrhoea Diarrhoea is defined as the passage of more than 200 g of stool daily and measurement of stool volume is helpful in confirming this. The most severe symptom in many patients is urgency of defecation, and faecal incontinence is a common event in acute and chronic diarrhoeal illnesses. Acute diarrhoea This is extremely common and is usually caused by faecal–oral transmission of bacteria or their toxins, viruses or parasites (Ch. 11). Infective diarrhoea is usually short-lived and patients who present with a history of diarrhoea lasting more than 10 days rarely have an infective cause. A variety of drugs, including antibiotics, cytotoxic drugs, PPIs and NSAIDs, may be responsible.

Chronic or relapsing diarrhoea The most common cause is irritable bowel syndrome (p. 824), which can present with increased frequency of defecation and loose, watery or pellety stools. Diarrhoea rarely occurs at night and is most severe before and after breakfast. At other times, the patient is constipated and there are other characteristic symptoms of irritable bowel syndrome. The stool often contains mucus but never blood, and 24-hour stool volume is less than 200 g. Chronic diarrhoea can be categorised as being caused by disease of the colon or small bowel, or to malabsorption (Box 21.18). Clinical presentation, examination of the stool, routine blood tests and imaging reveal a diagnosis in many cases. A series of negative investigations usually implies irritable bowel syndrome but some patients clearly have organic disease and need more extensive investigations. Malabsorption Diarrhoea and weight loss in patients with a normal diet are likely to be caused by malabsorption. The symptoms are diverse in nature and variable in severity. A few patients have apparently normal bowel habit but diarrhoea is usual and may be watery and voluminous. Bulky, pale and offensive stools that float in the toilet (steatorrhoea) signify fat malabsorption. Abdominal stops spontaneously but commonly recurs. Diagnosis is often difficult. Colonoscopy may reveal characteristic vascular spots and, in the acute phase, visceral angiography can show bleeding into the intestinal lumen and an abnormal large, draining vein. In some patients, diagnosis is achieved only by laparotomy with on-table colonoscopy. The treatment of choice is endoscopic thermal ablation but resection of the affected bowel may be required if bleeding continues. Bowel ischaemia due to occlusion of the inferior mesenteric artery can present with abdominal colic and rectal bleeding. It should be considered in patients (particularly the elderly) who have evidence of generalised atherosclerosis. The diagnosis is made at colonoscopy. Resection is required only in the presence of peritonitis. Meckel’s diverticulum with ectopic gastric epithelium may ulcerate and erode into a major artery. The diagnosis should be considered in children or adolescents who present with profuse or recurrent lower gastrointestinal bleeding. A Meckel’s 99mTc-pertechnetate scan is sometimes positive but the diagnosis is commonly made only by laparotomy, at which time the diverticulum is excised. Subacute or chronic lower gastrointestinal bleeding This can occur at all ages and is usually due to haemorrhoids or anal fissure. Haemorrhoidal bleeding is bright red and occurs during or after defecation. Proctoscopy can be used to make the diagnosis, but subjects who have altered bowel habit and those who present over the age of 40 years should undergo colonoscopy to exclude coexisting colorectal cancer. Anal fissure should be suspected when fresh rectal bleeding and anal pain occur during defecation. Major gastrointestinal bleeding of unknown cause In some patients who present with major gastrointestinal bleeding, upper endoscopy and colonoscopy fail to reveal a diagnosis. When severe life-threatening bleeding continues, urgent CT mesenteric angiography is indicated. This will usually identify the site if the bleeding rate exceeds 1 mL/min and then formal angiographic embolisation can often stop the bleeding. If angiography is negative or bleeding is less severe, push or double balloon enteroscopy can visualise the small intestine (Fig. 21.21) and treat the bleeding source. Wireless capsule endoscopy is often Fig. 21.21 Jejunal angiodysplastic lesion seen at enteroscopy in a patient with recurrent obscure bleeding.

 Pathophysiology Malabsorption results from abnormalities of the three processes that are essential to normal digestion: • Intraluminal maldigestion occurs when deficiency of bile or pancreatic enzymes results in inadequate solubilisation 21.18 Chronic or relapsing diarrhoea Colonic Malabsorption Small bowel Clinical features Blood and mucus in stool Cramping lower abdominal pain Steatorrhoea Undigested food in the stool Weight loss and nutritional disturbances Large-volume, watery stool Abdominal bloating Cramping mid-abdominal

pain Some causes Inflammatory bowel disease Microscopic colitis Neoplasia Ischaemia Irritable bowel syndrome Pancreatic: Chronic pancreatitis Cancer of pancreas Cystic fibrosis Enteropathy: Coeliac disease Tropical sprue Lymphoma Lymphangiectasia Crohn's disease VIPoma Drug-induced: NSAIDs Aminosalicylates SSRIs Investigations Faecal calprotectin Ileocolonoscopy with biopsies Faecal elastase Faecal calprotectin Ultrasound, CT and MRCP Stool volume Small-bowel biopsy Gut hormone profile Barium follow-through or small-bowel MRI Barium follow-through or small-bowel MRI (CT = computed tomography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; NSAIDs = non-steroidal anti-inflammatory drugs; SSRIs = selective serotonin re-uptake inhibitors; VIP = vasoactive intestinal polypeptide) distension, borborygmi, cramps, weight loss and undigested food in the stool may be present. Some patients complain only of malaise and lethargy. In others, symptoms related to deficiencies of specific vitamins, trace elements and minerals may occur (Fig. 21.22). Fig. 21.22 Possible physical consequences of malabsorption. Purpura and bruising (vitamins C, K) Poor wound healing (vitamin C, protein, zinc) Distension, steatorrhoea, watery diarrhoea Lethargy Depression Night blindness (vitamin A) Anaemia (iron, folate, B12) Angular stomatitis, glossitis (iron, folate, B12) Bleeding gums (vitamin C) Follicular hyperkeratosis (vitamin A) Acrodermatitis enteropathica (zinc) Koilonychia (iron) Paraesthesia, tetany (calcium, magnesium) Clubbing Osteomalacia, rickets (calcium, vitamin D) Muscle wasting (protein) Proximal myopathy (vitamin D) Peripheral neuropathy (B12) Peripheral oedema (hypoalbuminaemia)

cause. Routine blood tests may show one or more of the abnormalities listed in Box 21.19. Tests to confirm fat and protein malabsorption should be performed, as described on page 777. An approach to the investigation of malabsorption is shown in Figure 21.23. Weight loss Weight loss may be physiological, due to dieting, exercise, starvation, or the decreased nutritional intake that accompanies old age. Weight loss of more than 3 kg over 6 months is significant and often indicates the presence of an underlying disease. Hospital and general practice weight records may be valuable in confirming that weight loss has occurred, as may reweighing patients at intervals; sometimes weight is regained or stabilises in those with no obvious cause. Pathological weight loss can be due to psychiatric illness, systemic disease, gastrointestinal causes or advanced disease of many organ systems (Fig. 21.24). Physiological causes Weight loss can occur in the absence of serious disease in healthy individuals who have changes in physical activity or social circumstances. It may be difficult to be sure of this diagnosis in older patients, when the dietary history may be unreliable, and professional help from a dietitian is often valuable under these circumstances. Psychiatric illness Features of anorexia nervosa (p. 1203), bulimia (p. 1204) and affective disorders (p. 1198) may be apparent only after formal psychiatric input. Alcoholic patients lose weight as a consequence of self-neglect and poor dietary intake. Depression may cause weight loss. Systemic disease Chronic infections, including tuberculosis (p. 588), recurrent urinary or chest infections, and a range of parasitic and protozoan infections (Ch. 11), should be considered. A history of foreign travel, high-risk activities and specific features, such as fever, night sweats, rigors, productive cough and dysuria, must be sought. Promiscuous sexual activity and drug misuse suggest HIV-related illness (Ch. 12). Weight loss is a late feature of disseminated malignancy, but by the time the patient presents, other features of cancer are often present. Chronic inflammatory diseases, such as rheumatoid arthritis (p. 1021) and polymyalgia rheumatica (p. 1042), are often associated with weight loss. Gastrointestinal disease Almost any disease of the

gastrointestinal tract can cause weight loss. Dysphagia and gastric outflow obstruction (pp. 778 and 801) cause weight loss by reducing food intake. Malignancy at any site may cause weight loss by mechanical obstruction, anorexia or cytokine-mediated systemic effects. Malabsorption from pancreatic diseases (p. 837) or small bowel causes may lead to profound weight loss with specific nutritional deficiencies (p. 704). Inflammatory diseases, such as Crohn's disease or ulcerative colitis (p. 813), cause anorexia, fear of eating and loss of protein, blood and nutrients from the gut. Metabolic disorders and miscellaneous causes Weight loss may occur in association with metabolic disorders, as well as end-stage respiratory and cardiac disease. 21.19 Routine blood test abnormalities in malabsorption Haematology • Microcytic anaemia (iron deficiency) • Macrocytic anaemia (folate or B12 deficiency) • Increased prothrombin time (vitamin K deficiency) Biochemistry • Hypoalbuminaemia • Hypocalcaemia • Hypomagnesaemia • Hypophosphataemia • Low serum zinc Fig. 21.23 Investigation for suspected malabsorption. (CT = computed tomography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; 75SeHCAT = 75Se-homocholic acid taurine) Consider bile salt malabsorption • SeHCAT scan • Serum 7α-hydroxycholestenone Normal Normal Suspected malabsorption Clinical features of steatorrhoea • Blood tests (urea and electrolytes, immunoglobulins, Ca2+, Mg2+, full blood count, clotting, albumin, folate, B12, coeliac antibodies) Investigate small intestine • Duodenal biopsy • Barium studies or small bowel MRI • Faecal calprotectin • Lactulose/glucose hydrogen breath test Investigate pancreas • Pancreatic function tests, e.g. faecal elastase • Ultrasound scan/CT • MRCP and hydrolysis of nutrients. Fat and protein malabsorption results. This may also occur with small bowel bacterial overgrowth. • Mucosal malabsorption results from small bowel resection or conditions that damage the small intestinal epithelium, thereby diminishing the surface area for absorption and depleting brush border enzyme activity. • 'Post-mucosal' lymphatic obstruction prevents the uptake and transport of absorbed lipids into lymphatic vessels. Increased pressure in these vessels results in leakage into the intestinal lumen, leading to protein-losing enteropathy. Investigations Investigations should be performed both to confirm the presence of malabsorption and to determine the underlying

 Investigations In cases where the cause of weight loss is not obvious after thorough history taking and physical examination, or where an existing condition is considered unlikely, the following investigations are indicated: urinalysis for glucose, protein and blood; blood tests, including liver function tests, random blood glucose and thyroid function tests; CRP and ESR (may be raised in unsuspected infections, such as tuberculosis, connective tissue disorders and malignancy); and faecal calprotectin. Sometimes invasive tests, such as bone marrow aspiration or liver biopsy, may be necessary to identify conditions like cryptic miliary tuberculosis (p. 588). Rarely, abdominal and pelvic imaging by CT may be required, but before embarking on invasive or very costly investigations it is always worth revisiting the patient's history and reweighing at intervals. Constipation Constipation is defined as infrequent passage of hard stools. Patients may also complain of straining, a sensation of incomplete evacuation and either perianal or abdominal discomfort. Constipation may occur in many gastrointestinal and other medical disorders (Box 21.20). Clinical assessment and management The onset, duration and characteristics are important; for example, a neonatal onset suggests Hirschsprung's disease, while a recent change in bowel activity in middle age should raise the suspicion of an organic disorder, such as colonic carcinoma. The presence of rectal bleeding, pain and weight loss is important, as are excessive Fig. 21.24 Some important causes of weight loss. Chronic infection HIV/AIDS Tuberculosis Brucellosis Gut infestations Gastrointestinal Poor dentition Any cause of oral pain,

dysphagia Malabsorption Malignancy at any site Inflammatory bowel disease Chronic infection Cirrhosis Respiratory Chronic obstructive pulmonary disease Pulmonary tuberculosis Occult malignancy (especially small-cell carcinoma) Empyema Psychosocial Deprivation, starvation Eating disorders Depression, bipolar illness Bereavement Chronic pain/sleep deprivation Alcoholism Rheumatological Rheumatoid arthritis Mixed connective tissue disease Systemic sclerosis Systemic lupus erythematosus Renal Occult malignancy Chronic renal failure Salt-losing nephropathy Cardiac Congestive cardiac failure Infective endocarditis Endocrine Type 1 diabetes Thyrotoxicosis Addison's disease Neurodegenerative Parkinsonism Dementia Motor neuron disease 21.20 Causes of constipation Gastrointestinal causes Dietary • Lack of fibre and/or fluid intake Motility • Slow-transit constipation • Irritable bowel syndrome • Drugs (see below) • Chronic intestinal pseudo-obstruction Structural • Colonic carcinoma • Diverticular disease • Hirschsprung's disease Defecation • Anorectal disease (Crohn's, fissures, haemorrhoids) • Obstructed defecation Non-gastrointestinal causes Drugs • Opiates • Anticholinergics • Calcium antagonists • Iron supplements • Aluminium-containing antacids Neurological • Multiple sclerosis • Spinal cord lesions • Cerebrovascular accidents • Parkinsonism Metabolic/endocrine • Diabetes mellitus • Hypercalcaemia • Hypothyroidism • Pregnancy Others • Any serious illness with immobility, especially in the elderly • Depression

peritoneum is involved, when it becomes localised. Movement exacerbates the pain; abdominal rigidity and guarding occur. • Perforation. When a viscus perforates, pain starts abruptly; it is severe and leads to generalised peritonitis. • Obstruction. Pain is colicky, with spasms that cause the patient to writhe around and double up. Colicky pain that does not disappear between spasms suggests complicating inflammation. Initial clinical assessment If there are signs of peritonitis (guarding and rebound tenderness with rigidity), the patient should be resuscitated with oxygen, intravenous fluids and antibiotics. In other circumstances, further investigations are required (Fig. 21.25). Investigations Patients should have a full blood count, urea and electrolytes, glucose and amylase taken to look for evidence of dehydration, leucocytosis and pancreatitis. Urinalysis is useful in suspected renal colic and pyelonephritis. An erect chest X-ray may show air under the diaphragm, suggestive of perforation, and a plain abdominal film may show evidence of obstruction or ileus (see Fig. 21.11). An abdominal ultrasound may help if gallstones or renal stones are suspected. Ultrasonography is also useful in the detection of free fluid and any possible intra-abdominal abscess. Contrast studies, by either mouth or anus, are useful in the further evaluation of intestinal obstruction, and essential in the differentiation of pseudo-obstruction from mechanical large-bowel obstruction. Other investigations commonly used include CT (seeking evidence of pancreatitis, retroperitoneal collections or masses, including an aortic aneurysm or renal calculi) and angiography (mesenteric ischaemia). Diagnostic laparotomy should be considered when the diagnosis has not been revealed by other investigations. All patients must be carefully and regularly re-assessed (every 2–4 hours) so that any change in condition that might alter both the suspected diagnosis and clinical decision can be observed and acted on early. Management The general approach is to close perforations, treat inflammatory conditions with antibiotics or resection, and relieve obstructions. The speed of intervention and the necessity for surgery depend on the organ that is involved and on a number of other factors, straining, symptoms suggestive of irritable bowel syndrome, a history of childhood constipation and emotional distress. Careful examination contributes more to the diagnosis than extensive investigation. A search should be

made for general medical disorders, as well as signs of intestinal obstruction. Neurological disorders, especially spinal cord lesions, should be sought. Perineal inspection and rectal examination are essential and may reveal abnormalities of the pelvic floor (abnormal descent, impaired sensation), anal canal or rectum (masses, faecal impaction, prolapse). It is neither possible nor appropriate to investigate every person with constipation. Most respond to increased fluid intake, dietary fibre supplementation, exercise and the judicious use of laxatives. Middle-aged or elderly patients with a short history or worrying symptoms (rectal bleeding, pain or weight loss) must be investigated promptly, by either barium enema or colonoscopy. For those with simple constipation, investigation will usually proceed along the lines described below. Initial visit Digital rectal examination, proctoscopy and sigmoidoscopy (to detect anorectal disease), routine biochemistry, including serum calcium and thyroid function tests, and a full blood count should be carried out. If these are normal, a 1-month trial of dietary fibre and/or laxatives is justified. Next visit If symptoms persist, then examination of the colon by barium enema or CT colonography is indicated to look for structural disease. Further investigation If no cause is found and disabling symptoms are present, then specialist referral for investigation of possible dysmotility may be necessary. The problem may be one of infrequent desire to defecate ('slow transit') or else may result from neuromuscular incoordination and excessive straining ('functional obstructive defecation', p. 803). Intestinal marker studies, anorectal manometry, electrophysiological studies and magnetic resonance proctography can all be used to define the problem. Abdominal pain There are four types of abdominal pain: • Visceral. Gut organs are insensitive to stimuli such as burning and cutting but are sensitive to distension, contraction, twisting and stretching. Pain from unpaired structures is usually, but not always, felt in the midline. • Parietal. The parietal peritoneum is innervated by somatic nerves and its involvement by inflammation, infection or neoplasia causes sharp, well-localised and lateralised pain. • Referred pain. Gallbladder pain, for example, may be referred to the back or shoulder tip. • Psychogenic. Cultural, emotional and psychosocial factors influence everyone's experience of pain. In some patients, no organic cause can be found despite investigation, and psychogenic causes (depression or somatisation disorder) may be responsible (pp. 1198 and 1202). The acute abdomen This accounts for approximately 50% of all urgent admissions to general surgical units. The acute abdomen is a consequence of one or more pathological processes (Box 21.21): • Inflammation. Pain develops gradually, usually over several hours. It is initially rather diffuse until the parietal 21.21 Causes of acute abdominal pain Inflammation • Appendicitis • Diverticulitis • Cholecystitis • Pelvic inflammatory disease • Pancreatitis • Pyelonephritis • Intra-abdominal abscess Perforation/rupture • Peptic ulcer • Diverticular disease • Ovarian cyst • Aortic aneurysm Obstruction • Intestinal obstruction • Biliary colic • Ureteric colic Other (rare) • See Box 21.23

 treatment. The appendix can be removed through a conventional right iliac fossa skin crease incision or by laparoscopic techniques. Acute cholecystitis This can be successfully treated non-operatively but the high risk of recurrent attacks and the low morbidity of surgery have made early laparoscopic cholecystectomy the treatment of choice. Acute diverticulitis Conservative therapy is standard but if perforation has occurred, resection is advisable. Depending on peritoneal contamination and the state of the patient, primary anastomosis is preferable to a Hartmann's procedure (oversew of rectal stump and end-colostomy). Small bowel obstruction If the cause is obvious and surgery inevitable (such as with a strangulated hernia), an early operation is appropriate. If the suspected cause is adhesions from previous surgery, only those patients who do not resolve within the first 48 hours or who develop signs of strangulation (colicky pain becoming

constant, peritonitis, tachycardia, fever, leucocytosis) should have surgery. of which the presence or absence of peritonitis is the most important. A treatment summary of some of the more common surgical conditions follows. Acute appendicitis This should be treated by early surgery, since there is a risk of perforation and recurrent attacks with non-operative Fig. 21.25 Management of acute abdominal pain: an algorithm. Symptoms and signs of peritonitis Resuscitation Pain No clear evidence of peritonitis Blood tests ↑ Amylase/lipase Acute pancreatitis Free air Perforation Dilated loops of bowel Intestinal obstruction/ileus Gallstones and thickened gallbladder wall Cholecystitis Pseudo-obstruction CT scan Pancreatitis Abscess Aortic aneurysm Malignancy Erect chest X-ray Abdominal X-ray Ultrasound Contrast radiology Abnormality detected Abnormality detected Perforation Inconclusive investigations No diagnosis No free air No abnormality No abnormality No abnormality No abnormality Symptoms persist Symptoms settle Laparotomy Laparoscopy Observe 21.22 Acute abdominal pain in old age • Presentation: severity and localisation may blunt with age. Presentation may be atypical, e.g. with delirium, collapse and/or immobility. • Cancer: a more common cause of acute pain in those over 70 years of age than in those under 50 years. Older people with vague abdominal symptoms should therefore be carefully assessed. • Non-specific symptoms: intra-abdominal inflammatory conditions, such as diverticulitis, may present with non-specific symptoms, such as delirium or anorexia and relatively little abdominal tenderness. The reasons for this are not clear but may stem from altered sensory perception. • Outcome of abdominal surgery: determined by how frail the patient is and whether surgery is elective or emergency, rather than by chronological age.

Note should be made of the patient’s general demeanour, mood and emotional state, signs of weight loss, fever, jaundice or anaemia. If a thorough abdominal and rectal examination is normal, a careful search should be made for evidence of disease affecting other structures, particularly the vertebral column, spinal cord, lungs and cardiovascular system. Investigations will depend on the clinical features elicited during the history and examination: • Endoscopy and ultrasound are indicated for epigastric pain, and for dyspepsia and symptoms suggestive of gallbladder disease. • Colonoscopy is indicated for patients with altered bowel habit, rectal bleeding or features of obstruction suggesting colonic disease. • CT or MR angiography should be considered when pain is provoked by food in a patient with widespread atherosclerosis, since this may indicate mesenteric ischaemia. • Persistent symptoms require exclusion of colonic or small bowel disease. However, young patients with pain relieved by defecation, bloating and alternating bowel habit are likely to have irritable bowel syndrome (p. 824). Simple investigations (blood tests, faecal calprotectin and sigmoidoscopy) are sufficient in the absence of rectal bleeding, weight loss and abnormal physical findings. • Ultrasound, CT and faecal elastase are required for patients with upper abdominal pain radiating to the back. A history of alcohol misuse, weight loss and diarrhoea suggests chronic pancreatitis or pancreatic cancer. • Recurrent attacks of pain in the loins radiating to the flanks with urinary symptoms should prompt investigation for renal or ureteric stones by abdominal X-ray, ultrasound and computed tomography of the kidneys, ureters and bladder (CT KUB). • A past history of psychiatric disturbance, repeated negative investigations or vague symptoms that do not fit any disease or organ pattern suggest a psychological origin for the pain. Careful review of case notes and previous investigations, along with open and honest discussion with the patient, reduces the need for further cycles of unnecessary and invasive tests. Care must always be taken, however, not to miss rare pathology, such as acute intermittent porphyria (p. 378), or atypical

presentations of common diseases. Constant abdominal pain Patients with chronic pain that is constant or nearly always present usually have features to suggest the underlying diagnosis. No cause will be found in a minority, despite thorough investigation, leading to the diagnosis of ‘chronic functional abdominal pain’. In these patients, there appears to be abnormal CNS processing of normal visceral afferent sensory input and psychosocial factors are often operative (p. 1186); the most important tasks are to provide symptom control, if not relief, and to minimise the effects of the pain on social, personal and occupational life. Patients are best managed in specialised pain clinics where, in addition to psychological support, appropriate use of drugs, including tricyclic antidepressants, gabapentin or pregabalin, ketamine and opioids, may be necessary. Large bowel obstruction Pseudo-obstruction should be treated non-operatively. Some patients benefit from colonoscopic decompression but mechanical obstruction merits resection, usually with a primary anastomosis. Differentiation between the two is made by water-soluble contrast enema. Perforated peptic ulcer Surgical closure of the perforation is standard practice but some patients without generalised peritonitis can be treated non-operatively once a water-soluble contrast meal has confirmed spontaneous sealing of the perforation. Adequate and aggressive resuscitation with intravenous fluids, antibiotics and analgesia is mandatory before surgery. For a more detailed discussion of acute abdominal pain, the reader is referred to the sister volume of this text, Principles and Practice of Surgery. Chronic or recurrent abdominal pain It is essential to take a detailed history, paying particular attention to features of the pain and any associated symptoms (Boxes 21.23 and 21.24). 21.23 Extra-intestinal causes of chronic or recurrent abdominal pain Retroperitoneal • Aortic aneurysm • Malignancy • Lymphadenopathy • Abscess Psychogenic • Depression • Anxiety • Hypochondriasis • Somatisation Locomotor • Vertebral compression/fracture • Abdominal muscle strain Metabolic/endocrine • Diabetes mellitus • Acute intermittent porphyria • Hypercalcaemia Drugs/toxins • Glucocorticoids • Azathioprine • Lead • Alcohol Haematological • Sickle-cell disease • Haemolytic disorders Neurological • Spinal cord lesions • Tabes dorsalis • Radiculopathy 21.24 How to assess abdominal pain • Duration • Site and radiation • Severity • Precipitating and relieving factors (food, drugs, alcohol, posture, movement, defecation) • Nature (colicky, constant, sharp or dull, wakes patient at night) • Pattern (intermittent or continuous) • Associated features (vomiting, dyspepsia, altered bowel habit)

 Oral cancer may present in many ways (Box 21.26) and a high index of suspicion is required. All possible sources of local trauma or infection should be treated in patients with suspicious lesions and they should be reviewed after 2 weeks, with biopsy if the lesion persists. Small cancers can be resected but extensive surgery, with neck dissection to remove involved lymph nodes, may be necessary. Some patients can be treated with radical radiotherapy alone, and sometimes radiotherapy is also given after surgery to treat microscopic residual disease. Some tumours may be amenable to photodynamic therapy (PDT), avoiding the need for surgery. Candidiasis The yeast Candida albicans is a normal mouth commensal but it may proliferate to cause thrush. This occurs in babies, debilitated patients, people receiving glucocorticoid or antibiotic therapy, individuals with diabetes and immunosuppressed patients, especially those receiving cytotoxic therapy and those with HIV infection. White patches are seen on the tongue and buccal mucosa. Odynophagia or dysphagia suggests pharyngeal and oesophageal candidiasis. A clinical diagnosis is sufficient to instigate therapy, although brushings or biopsies can be obtained for mycological examination. Oral thrush is treated using nystatin or amphotericin suspensions or lozenges. Resistant cases or immunosuppressed patients may require oral fluconazole. Parotitis Parotitis is caused by viral or bacterial infection. Mumps causes a self-

limiting acute parotitis (p. 240). Bacterial parotitis usually occurs as a complication of major surgery. It is a consequence of dehydration and poor oral hygiene, and can be avoided by good post-operative care. Patients present with painful parotid swelling and this can be complicated by abscess formation. Broad-spectrum antibiotics are required, while surgical drainage is necessary for abscesses. Other causes of salivary gland enlargement are listed in Box 21.27. Diseases of the mouth and salivary glands Aphthous ulceration Aphthous ulcers are superficial and painful; they occur in any part of the mouth. Recurrent ulcers afflict up to 30% of the population and are particularly common in women prior to menstruation. The cause is unknown, but in severe cases other causes of oral ulceration must be considered (Box 21.25). Biopsy is occasionally necessary for diagnosis. Management is with topical glucocorticoids (such as 0.1% triamcinolone in Orabase) or choline salicylate (8.7%) gel. Symptomatic relief is achieved using local anaesthetic mouthwashes. Rarely, patients with very severe, recurrent aphthous ulcers may need oral glucocorticoids. 21.26 Symptoms and signs of oral cancer • Solitary ulcer without precipitant, e.g. local trauma • Solitary white patch (‘leukoplakia’) that fails to wipe off • Solitary red patch • Fixed lump • Lip numbness in absence of trauma or infection • Trismus (pain/difficulty in opening the mouth) • Cervical lymphadenopathy 21.25 Causes of oral ulceration Aphthous • Idiopathic • Premenstrual Infection • Fungal (candidiasis) • Viral (herpes simplex, HIV) • Bacterial, including syphilis, tuberculosis Gastrointestinal diseases • Crohn’s disease • Coeliac disease Dermatological conditions • Lichen planus • Immunobullous disorders (p. 1255) • Dermatitis herpetiformis • Erythema multiforme Drugs • Nicorandil, NSAIDs, methotrexate, penicillamine, losartan, ACE inhibitors • Stevens–Johnson syndrome (pp. 1254 and 1264) • Cytotoxic drugs Systemic diseases • Systemic lupus erythematosus (p. 1034) • Behçet’s disease (p. 1043) Neoplasia • Carcinoma • Leukaemia • Kaposi’s sarcoma (ACE = angiotensin-converting enzyme; NSAIDs = non-steroidal anti-inflammatory drugs) 21.27 Causes of salivary gland swelling • Infection: Mumps Bacterial (post-operative) • Calculi • Sjögren’s syndrome (p. 1038) • Sarcoidosis • Tumours: Benign: pleomorphic adenoma (95% of cases) Intermediate: mucoepidermoid tumour Malignant: carcinoma Oral cancer Squamous carcinoma of the oral cavity is common worldwide and the incidence has increased by 25% in the last decade in the UK. The mortality rate is around 50%, largely as a result of late diagnosis. Poor diet, alcohol excess and smoking or tobacco chewing are the traditional risk factors but high-risk, oncogenic strains of human papillomavirus (HPV-16 and HPV-18) have been identified as being responsible for much of the recent increase in incidence, especially in cases affecting the base of tongue, soft palate and tonsils. In parts of Asia, the disease is common among people who chew areca nuts wrapped in leaves of the betel plant (‘betel nuts’).

Gastric contents Gastric acid is the most important oesophageal irritant and there is a close relationship between acid exposure time and symptoms. Pepsin and bile also contribute to mucosal injury. Defective gastric emptying Gastric emptying is delayed in patients with gastro-oesophageal reflux disease. The reason is unknown. Increased intra-abdominal pressure Pregnancy and obesity are established predisposing causes. Weight loss may improve symptoms. Dietary and environmental factors Dietary fat, chocolate, alcohol, tea and coffee relax the lower oesophageal sphincter and may provoke symptoms. The foods that trigger symptoms vary widely between affected individuals. Patient factors Visceral sensitivity and patient vigilance play a role in determining symptom severity and consulting behaviour in individual patients. Clinical features The major symptoms are heartburn and regurgitation, often provoked by bending, straining or lying

down. ‘Waterbrash’, which is salivation due to reflex salivary gland stimulation as acid enters the gullet, is often present. The patient is often overweight. Some patients are woken at night by choking as refluxed fluid Diseases of the oesophagus Gastro-oesophageal reflux disease Gastro-oesophageal reflux resulting in heartburn affects approximately 30% of the general population. Pathophysiology Occasional episodes of gastro-oesophageal reflux are common in healthy individuals. Reflux is normally followed by oesophageal peristaltic waves that efficiently clear the gullet, alkaline saliva neutralises residual acid and symptoms do not occur. Gastrooesophageal reflux disease develops when the oesophageal mucosa is exposed to gastroduodenal contents for prolonged periods of time, resulting in symptoms and, in a proportion of cases, oesophagitis. Several factors are known to be involved in the development of gastro-oesophageal reflux disease and these are shown in Figure 21.26. Abnormalities of the lower oesophageal sphincter The lower oesophageal sphincter is tonically contracted under normal circumstances, relaxing only during swallowing (p. 766). Some patients with gastro-oesophageal reflux disease have reduced lower oesophageal sphincter tone, permitting reflux when intra-abdominal pressure rises. In others, basal sphincter tone is normal but reflux occurs in response to frequent episodes of inappropriate sphincter relaxation. Hiatus hernia Hiatus hernia (Box 21.29 and Fig. 21.27) causes reflux because the pressure gradient is lost between the abdominal and thoracic cavities, which normally pinches the hiatus. In addition, the oblique angle between the cardia and oesophagus disappears. Many patients who have large hiatus hernias develop reflux symptoms but the relationship between the presence of a hernia and symptoms is poor. Hiatus hernia is very common in individuals who have no symptoms, and some symptomatic patients have only a very small or no hernia. Nevertheless, almost all patients who develop oesophagitis, Barrett’s oesophagus or peptic strictures have a hiatus hernia. Delayed oesophageal clearance Defective oesophageal peristaltic activity is commonly found in patients who have oesophagitis. It is a primary abnormality, since it persists after oesophagitis has been healed by acid-suppressing drug therapy. Poor oesophageal clearance leads to increased acid exposure time. 21.28 Oral health in old age • Dry mouth: affects around 40% of healthy older people. • Gustatory and olfactory sensation: declines and chewing power is diminished. • Salivation: baseline salivary flow falls but stimulated salivation is unchanged. • Root caries and periodontal disease: common partly because oral hygiene deteriorates with increasing frailty. • Bacteraemia and sepsis: may complicate Gram-negative anaerobic infection in the periodontal pockets of the very frail. Fig. 21.26 Factors associated with the development of gastrooesophageal reflux disease. Acid-pepsin (bile) Delayed gastric emptying Hiatus hernia Defective oesophageal clearance Abnormal lower oesophageal sphincter • Reduced tone • Inappropriate relaxation Increased intra-abdominal pressure Obesity Dietary factors 21.29 Important features of hiatus hernia • Herniation of the stomach through the diaphragm into the chest • Occurs in 30% of the population over the age of 50 years • Often asymptomatic • Heartburn and regurgitation can occur • Gastric volvulus may complicate large hernias

 may be important in the pathogenesis. The molecular events underlying progression of Barrett’s oesophagus to dysplasia and cancer are incompletely understood but inactivation of the tumour suppression protein p16 by loss of heterozygosity or promoter hypermethylation is a key event, followed by somatic inactivation of TP53, which promotes aneuploidy and tumour progression. Studies are in progress to develop biomarkers that will allow detection of those at higher cancer risk. Diagnosis This requires multiple systematic biopsies to maximise the chance of detecting intestinal metaplasia and/or dysplasia. Management Neither potent acid suppression nor anti-reflux surgery stops progression or induces regression of

Barrett’s Fig. 21.27 Types of hiatus hernia. A Rolling or para-oesophageal. Inset: Barium meal showing a large para-oesophageal hernia with intrathoracic stomach. B Sliding. Inset: Barium meal showing a gastric volvulus (small arrows) complicating a sliding hiatus hernia (large arrow). Lower oesophageal sphincter Lower oesophageal sphincter Diaphragm Diaphragm A B Fig. 21.28 Severe reflux oesophagitis. There is near-circumferential superficial ulceration and inflammation extending up the gullet. irritates the larynx. Others develop odynophagia or dysphagia. A variety of other features have been described, such as atypical chest pain that may be severe and can mimic angina; it may be due to reflux-induced oesophageal spasm. Others include hoarseness (‘acid laryngitis’), recurrent chest infections, chronic cough and asthma. The true relationship of these features to gastro-oesophageal reflux disease remains unclear. Complications Oesophagitis A range of endoscopic findings is recognised, from mild redness to severe bleeding ulceration with stricture formation, although appearances may be completely normal (Fig. 21.28). There is a poor correlation between symptoms and histological and endoscopic findings. Barrett’s oesophagus Barrett’s oesophagus is a pre-malignant condition, in which the normal squamous lining of the lower oesophagus is replaced by columnar mucosa (columnar lined oesophagus; CLO) that may contain areas of intestinal metaplasia (Fig. 21.29). It is an adaptive response to chronic gastro-oesophageal reflux and is found in 10% of patients undergoing gastroscopy for reflux symptoms. Community-based epidemiological studies suggest that the true prevalence may be up to 1.5–5% of the population, as the condition is often asymptomatic until discovered when the patient presents with oesophageal cancer. The relative risk of oesophageal cancer is increased 40–120-fold but the absolute risk is low (0.1–0.5% per year). The epidemiology and aetiology of Barrett’s oesophagus are poorly understood. The prevalence is increasing, and it is more common in men (especially white), the obese and those over 50 years of age. It is weakly associated with smoking but not alcohol intake. The risk of cancer seems to relate to the severity and duration of reflux rather than the presence of Barrett’s oesophagus per se, and it has been suggested that duodenogastro-oesophageal reflux of bile, pancreatic enzymes and pepsin, as well as gastric acid,

Diagnosis is by endoscopy, when biopsies of the stricture can be taken to exclude malignancy. Endoscopic balloon dilatation or bouginage is helpful. Subsequently, long-term therapy with a PPI drug at full dose should be started to reduce the risk of recurrent oesophagitis and stricture formation. The patient should be advised to chew food thoroughly and it is important to ensure adequate dentition. Gastric volvulus Occasionally, a massive intrathoracic hiatus hernia may twist on itself, leading to a gastric volvulus. This gives rise to complete oesophageal or gastric obstruction and the patient presents with severe chest pain, vomiting and dysphagia. The diagnosis is made by chest X-ray (air bubble in the chest) and barium swallow (see Fig. 21.27B). Most cases spontaneously resolve but recurrence is common, and surgery is usually advised after the acute episode has been treated by nasogastric decompression. Investigations Young patients who present with typical symptoms of gastrooesophageal reflux, without worrying features such as dysphagia, weight loss or anaemia, can be treated empirically without investigation. Investigation is advisable if patients present over the age of 50–55 years, if symptoms are atypical or if a complication is suspected. Endoscopy is the investigation of choice. This is performed to exclude other upper gastrointestinal diseases that can mimic gastro-oesophageal reflux and to identify complications. A normal endoscopy in a patient with compatible symptoms should not preclude treatment for gastro-oesophageal reflux disease. Twenty-four-hour pH monitoring is indicated if the

diagnosis is unclear or surgical intervention is under consideration. This involves tethering a slim catheter with a terminal radiotelemetry pH-sensitive probe above the gastro-oesophageal junction. The intraluminal pH is recorded while the patient undergoes normal activities, and episodes of symptoms are noted and related to pH. A pH of less than 4 for more than 6–7% of the study time is diagnostic of reflux disease. In a few patients with difficult reflux, impedance testing can detect weakly acidic or alkaline reflux that is not revealed by standard pH testing. Management A treatment algorithm for gastro-oesophageal reflux is outlined in Figure 21.30. Lifestyle advice should be given, including weight loss, avoidance of dietary items that the patient finds worsen symptoms, elevation of the bed head in those who experience nocturnal symptoms, avoidance of late meals and cessation of smoking. Patients who fail to respond to these measures should be offered PPIs, which are usually effective in resolving symptoms and healing oesophagitis. Recurrence of symptoms is common when therapy is stopped and some patients require life-long treatment at the lowest acceptable dose. When dysmotility features are prominent, domperidone can be helpful. There is no evidence that H. pylori eradication has any therapeutic value. Proprietary antacids and alginates can also provide symptomatic benefit. H2-receptor antagonist drugs relieve symptoms without healing oesophagitis. Long-term PPI therapy is associated with reduced absorption of iron, B12 and magnesium, and a small but increased risk of osteoporosis and fractures (odds ratio 1.2–1.5). The drugs also predispose to enteric infections with Salmonella, Campylobacter and possibly Clostridium difficile, and have recently been shown to have an undesirable impact on the composition of the gut oesophagus, and treatment is indicated only for symptoms of reflux or complications, such as stricture. Endoscopic therapies, such as radiofrequency ablation or photodynamic therapy, can induce regression but at present are used only for those with dysplasia or intramucosal cancer. Regular endoscopic surveillance can detect dysplasia at an early stage and may improve survival but, because most Barrett’s oesophagus is undetected until cancer develops, surveillance strategies are unlikely to influence the overall mortality rate of oesophageal cancer. Surveillance is expensive and cost-effectiveness studies have been conflicting. It is currently recommended that patients with Barrett’s oesophagus with intestinal metaplasia, but without dysplasia, should undergo endoscopy at 3–5-yearly intervals if the length of the Barrettic segment is less than 3 cm and at 2–3-yearly intervals if the length is greater than 3 cm. Those with low-grade dysplasia should be endoscoped at 6-monthly intervals. For those with high-grade dysplasia or intramucosal carcinoma, the treatment options are either oesophagectomy or endoscopic therapy, with a combination of endoscopic resection of any visibly abnormal areas and radiofrequency ablation of the remaining Barrett’s mucosa, as an ‘organ-preserving’ alternative to surgery. These cases should be discussed in a multidisciplinary team meeting and managed in specialist centres. Anaemia Iron deficiency anaemia can occur as a consequence of occult blood loss from long-standing oesophagitis. Most patients have a large hiatus hernia and bleeding can stem from subtle erosions in the neck of the sac (‘Cameron lesions’). Nevertheless, hiatus hernia is very common and other causes of blood loss, particularly colorectal cancer, must be considered in anaemic patients, even when endoscopy reveals oesophagitis. Benign oesophageal stricture Fibrous strictures can develop as a consequence of longstanding oesophagitis, especially in the elderly and those with poor oesophageal peristaltic activity. The typical presentation is with dysphagia that is worse for solids than for liquids. Bolus obstruction following ingestion of meat causes absolute dysphagia. A history of heartburn is common but not invariable; many elderly patients presenting with strictures have no preceding heartburn. Fig. 21.29 Barrett’s oesophagus. Tongues of pink columnar mucosa are seen extending upwards above the oesophago-gastric junction.

794 • GASTROENTEROLOGY is conservative, based on analgesia and nutritional support; vomiting and endoscopy should be avoided because of the high risk of oesophageal perforation. After the acute phase, a barium swallow should be performed to demonstrate the extent of stricture formation. Endoscopic dilatation is usually necessary but it is difficult and hazardous because strictures are often long, tortuous and easily perforated. Drugs Potassium supplements and NSAIDs may cause oesophageal ulcers when the tablets are trapped above an oesophageal stricture. Liquid preparations of these drugs should be used in such patients. Bisphosphonates cause oesophageal ulceration and should be used with caution in patients with known oesophageal disorders. Eosinophilic oesophagitis This is more common in children but increasingly recognised in young adults. It occurs more often in atopic individuals and is characterised by eosinophilic infiltration of the oesophageal mucosa. Patients present with dysphagia or food bolus obstruction more often than heartburn, and other symptoms, such as chest pain and vomiting, may be present. Endoscopy is usually normal but mucosal rings (that sometimes need endoscopic dilatation), strictures or a narrow-calibre oesophagus can occur. Children may respond to elimination diets but these are less successful in adults, who should first be treated with PPIs. The condition can be treated with 8–12 weeks of therapy with topical glucocorticoids, such as fluticasone or betamethasone. The usual approach is to prescribe a metered-dose inhaler but to tell the patient to spray this into the mouth and swallow it rather than inhale it. Refractory symptoms sometimes respond to montelukast, a leukotriene inhibitor. Motility disorders Pharyngeal pouch This occurs because of incoordination of swallowing within the pharynx, which leads to herniation through the cricopharyngeus muscle and formation of a pouch. It is rare, affecting 1 in 100 000 people; it usually develops in middle life but can arise at any age. Many patients have no symptoms but regurgitation, halitosis and dysphagia can be present. Some notice gurgling in the throat after swallowing. The investigation of choice is a barium swallow (see Fig. 21.12A), which demonstrates the pouch and reveals incoordination of swallowing, often with pulmonary aspiration. Endoscopy may be hazardous, since the instrument may enter and perforate the pouch. Surgical myotomy (‘diverticulotomy’), with or without resection of the pouch, is indicated in symptomatic patients. Achalasia of the oesophagus Pathophysiology Achalasia is characterised by: • a hypertonic lower oesophageal sphincter, which fails to relax in response to the swallowing wave • failure of propagated oesophageal contraction, leading to progressive dilatation of the gullet. The cause is unknown. Defective release of nitric oxide by inhibitory neurons in the lower oesophageal sphincter has been reported, and there is degeneration of ganglion cells within the microbiota. Long-term therapy increases the risk of Helicobacterassociated progression of gastric mucosal atrophy (see below) and H. pylori eradication is advised in patients requiring PPIs for more than 1 year. Patients who fail to respond to medical therapy, those who are unwilling to take long-term PPIs and those whose major symptom is severe regurgitation should be considered for laparoscopic anti-reflux surgery (see Principles and Practice of Surgery). Although heartburn and regurgitation are alleviated in most patients, a small minority develop complications, such as inability to vomit and abdominal bloating (‘gas-bloat’ syndrome’). Other causes of oesophagitis Infection Oesophageal candidiasis occurs in debilitated patients and those taking broad-spectrum antibiotics or cytotoxic drugs. It is a particular problem in patients with HIV/AIDS, who are also susceptible to a spectrum of other oesophageal infections (p. 316). Corrosives Suicide attempt by ingestion of strong household bleach or battery acid is followed by painful burns of the mouth and pharynx and by extensive erosive oesophagitis (p. 147). This may be complicated by oesophageal perforation with mediastinitis and by stricture formation. At the time of presentation, treatment Fig. 21.30 Treatment of gastro-oesophageal reflux disease: a ‘step-down’ approach. Symptoms

Antacids/alginates Proton pump inhibitor at full dose Good response Poor response or side-effects Reconsider diagnosis Consider pH monitoring Normal Positive Proton pump inhibitor at maintenance dose H2-receptor antagonists Antacids Fundoplication 21.30 Gastro-oesophageal reflux disease in old age • Prevalence: higher. • Severity of symptoms: does not correlate with the degree of mucosal inflammation. • Complications: late complications, such as peptic strictures or bleeding from oesophagitis, are more common. • Recurrent pneumonia: consider aspiration from occult gastrooesophageal reflux disease.

invasive than endoscopic dilatation. Both pneumatic dilatation and myotomy may be complicated by gastro-oesophageal reflux, and this can lead to severe oesophagitis because oesophageal clearance is so poor. For this reason, Heller's myotomy is accompanied by a partial fundoplication anti-reflux procedure. PPI therapy is often necessary after surgery. Other oesophageal motility disorders Diffuse oesophageal spasm presents in late middle age with episodic chest pain that may mimic angina but is sometimes accompanied by transient dysphagia. Some cases occur in response to gastro-oesophageal reflux. Treatment is based on the use of PPI drugs when gastro-oesophageal reflux is present. Oral or sublingual nitrates or nifedipine may relieve attacks of pain. The results of drug therapy are often disappointing, as are the alternatives: pneumatic dilatation and surgical myotomy. 'Nutcracker' oesophagus is a condition in which extremely forceful peristaltic activity leads to episodic chest pain and dysphagia. Treatment is with nitrates or nifedipine. Some patients present with oesophageal motility disorders that do not fit into a specific disease entity. The patients are usually elderly and present with dysphagia and chest pain. Manometric abnormalities, ranging from poor peristalsis to spasm, occur. Treatment is with dilatation and/or vasodilators for chest pain. Secondary causes of oesophageal dysmotility In systemic sclerosis or CREST syndrome (p. 1037), the muscle of the oesophagus is replaced by fibrous tissue, which causes failure of peristalsis leading to heartburn and dysphagia. Oesophagitis is often severe and benign fibrous strictures occur. These patients require long-term therapy with PPIs. Dermatomyositis, rheumatoid arthritis and myasthenia gravis may also cause dysphagia. Benign oesophageal stricture Benign oesophageal stricture is usually a consequence of gastro-oesophageal reflux disease (Box 21.31) and occurs most often in elderly patients who have poor oesophageal clearance. Rings, caused by submucosal fibrosis, are found at the oesophago-gastric junction ('Schatzki ring') and cause intermittent sphincter and the body of the oesophagus. Loss of the dorsal vagal nuclei within the brainstem can be demonstrated in later stages. Infection with Trypanosoma cruzi in Chagas' disease (p. 279) causes a syndrome that is clinically indistinguishable from achalasia. Clinical features The presentation is with dysphagia. This develops slowly, is initially intermittent, and is worse for solids and eased by drinking liquids and by standing and moving around after eating. Heartburn does not occur because the closed oesophageal sphincter prevents gastro-oesophageal reflux. Some patients experience episodes of chest pain due to oesophageal spasm. As the disease progresses, dysphagia worsens, the oesophagus empties poorly and nocturnal pulmonary aspiration develops. Achalasia predisposes to squamous carcinoma of the oesophagus. Investigations Endoscopy should always be carried out because carcinoma of the cardia can mimic the presentation and radiological and manometric features of achalasia ('pseudo-achalasia'). A barium swallow shows tapered narrowing of the lower oesophagus and, in late disease, the oesophageal body is dilated, aperistaltic and food-filled (Fig. 21.31A). Manometry confirms the high-pressure, non-relaxing lower oesophageal sphincter with

poor contractility of the oesophageal body (Fig. 21.31B). Management Endoscopic Forceful pneumatic dilatation using a 30–35-mm-diameter, fluoroscopically positioned balloon disrupts the oesophageal sphincter and improves symptoms in 80% of patients. Some patients require more than one dilatation but those needing frequent dilatation are best treated surgically. Endoscopically directed injection of botulinum toxin into the lower oesophageal sphincter induces clinical remission but relapse is common. Recently, a complex endoscopic technique has been developed in specialist centres (peroral endoscopic myotomy, POEM). Surgical Surgical myotomy (Heller's operation), performed either laparoscopically or as an open operation, is effective but is more Fig. 21.31 Achalasia. A X-ray showing a dilated, barium-filled oesophagus (O) with fluid level and distal tapering, and a closed lower oesophageal sphincter (LOS). (D = diaphragm) B High-resolution manometry in achalasia showing absence of peristaltic swallowing wave in oesophageal body (black arrows) and raised LOS pressure with failure of relaxation on swallowing (white arrow). Compare with normal appearances in Figure 21.1 (p. 766). Time (secs) LOS D O A B

796 • GASTROENTEROLOGY spread and local invasion (Fig. 21.33). Invasion of the aorta, major airways or coeliac axis usually precludes surgery, but patients with resectable disease on imaging should undergo EUS to determine the depth of penetration of the tumour into the oesophageal wall and to detect locoregional lymph node dysphagia, often starting in middle age. A post-cricoid web is a rare complication of iron deficiency anaemia (Paterson–Kelly or Plummer–Vinson syndrome), and may be complicated by the development of squamous carcinoma. Benign strictures can be treated by endoscopic dilatation, in which wire-guided bougies or balloons are used to disrupt the fibrous tissue of the stricture. Tumours of the oesophagus Benign tumours The most common is a leiomyoma. This is usually asymptomatic but may cause bleeding or dysphagia. Carcinoma of the oesophagus Squamous oesophageal cancer (Box 21.32) is relatively rare in Caucasians (4 : 100 000) but is more common in Iran, parts of Africa and China (200 : 100 000). Squamous cancer can occur in any part of the oesophagus and almost all tumours in the upper oesophagus are squamous cancers. Adenocarcinomas typically arise in the lower third of the oesophagus from Barrett's oesophagus or from the cardia of the stomach. The incidence is increasing and is now approximately 5: 100 000 in the UK; this is possibly because of the high prevalence of gastro-oesophageal reflux and Barrett's oesophagus in Western populations. Despite modern treatment, the overall 5-year survival of patients presenting with oesophageal cancer is only 13%. Clinical features Most patients have a history of progressive, painless dysphagia for solid foods. Others present acutely because of food bolus obstruction. In the late stages, weight loss is often extreme; chest pain or hoarseness suggests mediastinal invasion. Fistulation between the oesophagus and the trachea or bronchial tree leads to coughing after swallowing, pneumonia and pleural effusion. Physical signs may be absent but, even at initial presentation, cachexia, cervical lymphadenopathy or other evidence of metastatic spread is common. Investigations The investigation of choice is upper gastrointestinal endoscopy (Fig. 21.32) with biopsy. A barium swallow demonstrates the site and length of the stricture but adds little useful information. Once a diagnosis has been made, investigations should be performed to stage the tumour and define operability. Thoracic and abdominal CT, often combined with positron emission tomography (PET-CT), should be carried out to identify metastatic 21.31 Causes of oesophageal stricture • Gastro-oesophageal reflux disease • Webs and rings • Carcinoma of the oesophagus or cardia • Eosinophilic oesophagitis • Extrinsic compression from bronchial carcinoma • Corrosive ingestion • Post-operative scarring following oesophageal resection • Post-radiotherapy • Following long-term nasogastric intubation • Bisphosphonates Fig. 21.32 Adenocarcinoma of the lower oesophagus. A polypoidal

adenocarcinoma in association with Barrett’s oesophagus. Fig. 21.33 Positron emission tomography–computed tomography (PET-CT) staging of oesophageal carcinoma. Whole-body PET scan showing avid uptake in the primary tumour (thick arrow) but also in distant paratracheal (superior thin arrow) and gastro-oesophageal (inferior thin arrow) lymph nodes. 21.32 Squamous carcinoma: aetiological factors • Smoking • Alcohol excess • Chewing betel nuts or tobacco • Achalasia of the oesophagus • Coeliac disease • Post-cricoid web • Post-caustic stricture • Tylosis (familial hyperkeratosis of palms and soles)

Spontaneous oesophageal perforation (‘Boerhaave’s syndrome’) results from forceful vomiting and retching. Severe chest pain and shock occur as oesophago-gastric contents enter the mediastinum and thoracic cavity. Subcutaneous emphysema, pleural effusions and pneumothorax develop. The diagnosis can be made using a water-soluble contrast swallow but, in difficult cases, both CT and careful endoscopy (usually in an intubated patient) may be required. Treatment is surgical. Delay in diagnosis is a key factor in the high mortality associated with this condition. Diseases of the stomach and duodenum Gastritis Gastritis is a histological diagnosis, although it can also be recognised at endoscopy. Acute gastritis Acute gastritis is often erosive and haemorrhagic. Neutrophils are the predominant inflammatory cell in the superficial epithelium. Many cases result from alcohol, aspirin or NSAID ingestion (Box 21.33). Acute gastritis often produces no symptoms but may cause dyspepsia, anorexia, nausea or vomiting, and haematemesis or melaena. Many cases resolve quickly and do not merit investigation; in others, endoscopy and biopsy may be necessary to exclude peptic ulcer or cancer. Treatment should be directed at the underlying cause. Short-term symptomatic therapy with antacids, and acid suppression using PPIs, prokinetics (domperidone) or antiemetics (metoclopramide) may be necessary. Chronic gastritis due to Helicobacter pylori infection This is the most common cause of chronic gastritis (Box 21.33). The predominant inflammatory cells are lymphocytes and plasma cells. Correlation between symptoms and endoscopic or pathological findings is poor. Most patients are asymptomatic and do not require treatment but patients with dyspepsia may benefit from H. pylori eradication. Autoimmune chronic gastritis This involves the body of the stomach but spares the antrum; it results from autoimmune damage to parietal cells. The histological features are diffuse chronic inflammation, atrophy and loss of fundic glands, intestinal metaplasia and sometimes hyperplasia of enterochromaffin-like (ECL) cells. Circulating antibodies to parietal cell and intrinsic factor may be present. In some patients, the degree of gastric atrophy is severe and loss of intrinsic factor secretion leads to pernicious anaemia (p. 944). The gastritis itself is usually asymptomatic. Some patients have evidence of other organ-specific autoimmunity, particularly thyroid disease. In the long term, there is a two- to threefold increase in the risk of gastric cancer (see also p. 803). Ménétrier’s disease In this rare condition, the gastric pits are elongated and tortuous, with replacement of the parietal and chief cells by mucus-secreting cells. The cause is unknown but there is excessive production of transforming growth factor alpha (TGF-α). As a result, the involvement (Fig. 21.34). These investigations will define the TNM stage of the disease (p. 1322). Management The treatment of choice is surgery if the patient presents at a point at which resection is possible. For very early superficial tumours, endoscopic submucosal dissection may offer an alternative to surgery but is not widely used outside of Japan and Korea. Patients with tumours that have extended beyond the wall of the oesophagus (T3) or that have lymph node involvement (N1) carry a 5-year survival of around 10%. This figure improves significantly, however, if the tumour is confined to the

oesophageal wall and there is no spread to lymph nodes. Overall survival following ‘potentially curative’ surgery (all macroscopic tumour removed) is about 30% at 5 years but recent studies have suggested that this can be improved by neoadjuvant chemotherapy. Although squamous carcinomas are radiosensitive, radiotherapy alone is associated with a 5-year survival of only 5% but combined chemoradiotherapy for these tumours can achieve 5-year survival rates of 25–30%. Approximately 70% of patients have extensive disease at presentation; in these, treatment is palliative and should focus on relief of dysphagia and pain. Endoscopic laser therapy or self-expanding metallic stents can be used to improve swallowing. Palliative radiotherapy may induce shrinkage of both squamous cancers and adenocarcinomas but symptomatic response may be slow. Quality of life can be improved by nutritional support and appropriate analgesia. Perforation of the oesophagus The most common cause is endoscopic perforation complicating dilatation or intubation. Malignant, corrosive or post-radiotherapy strictures are more likely to be perforated than peptic strictures. A perforated peptic stricture is managed conservatively using broad-spectrum antibiotics and parenteral nutrition; most cases heal within days. Malignant, caustic and radiotherapy stricture perforations require resection or stenting. Fig. 21.34 Endoscopic ultrasound staging of oesophageal carcinoma. There is a superficial adenocarcinoma of the oesophagus (T). The submucosa (white band, white arrows) is not involved but there is a small involved local lymph node (white arrow, inset). The tumour is therefore staged T1a, N1. T

798 • GASTROENTEROLOGY in the UK approximately 50% of people over the age of 50 years are infected. In the developing world infection is more common, affecting up to 90% of adults. These infections are probably acquired in childhood by person-to-person contact. The vast majority of colonised people remain healthy and asymptomatic, and only a minority develop clinical disease. Around 90% of duodenal ulcer patients and 70% of gastric ulcer patients are infected with H. pylori. The remaining 30% of gastric ulcers are caused by NSAIDs and this proportion is increasing in Western countries as a result of H. pylori eradication strategies. H. pylori is Gram-negative and spiral, and has multiple flagella at one end, which make it motile, allowing it to burrow and live beneath the mucus layer adherent to the epithelial surface. It uses an adhesin molecule (BabA) to bind to the Lewis b antigen on epithelial cells. Here the surface pH is close to neutral and any acidity is buffered by the organism’s production of the enzyme urease. This produces ammonia from urea and raises the pH around the bacterium and between its two cell membrane layers. H. pylori exclusively colonises gastric-type epithelium and is found in the duodenum only in association with patches of gastric metaplasia. It causes chronic gastritis by provoking a local inflammatory response in the underlying epithelium (Fig. 21.35). This depends on numerous factors, notably expression of bacterial cagA and vacA genes. The CagA gene product is injected into epithelial cells, interacting with numerous cell-signalling pathways involved in cell replication and apoptosis. H. pylori strains expressing CagA (CagA+) are more often associated with disease than CagA− strains. Most strains also secrete a large pore-forming protein called VacA, which causes increased cell permeability, efflux of micronutrients from the epithelium, induction of apoptosis and suppression of local immune cell activity. Several forms of VacA exist and pathology is most strongly associated with the s1/ml form of the toxin. The distribution and severity of H. pylori–induced gastritis determine the clinical outcome. In most people, H. pylori causes a mild pangastritis with little effect on acid secretion and the majority develop no significant clinical outcomes. In a minority (up mucosal folds of the body and fundus are greatly enlarged. Most patients are hypochlorhydric. While some patients have upper gastrointestinal symptoms, the majority present in middle or old age with protein-losing enteropathy (p. 811) due to exudation

from the gastric mucosa. Endoscopy shows enlarged, nodular and coarse folds, although biopsies may not be deep enough to show all the histological features. Treatment with antisecretory drugs, such as PPIs with or without octreotide, may reduce protein loss and H. pylori eradication may be effective, but unresponsive patients require partial gastrectomy. Peptic ulcer disease The term ‘peptic ulcer’ refers to an ulcer in the lower oesophagus, stomach or duodenum, in the jejunum after surgical anastomosis to the stomach or, rarely, in the ileum adjacent to a Meckel’s diverticulum. Ulcers in the stomach or duodenum may be acute or chronic; both penetrate the muscularis mucosae but the acute ulcer shows no evidence of fibrosis. Erosions do not penetrate the muscularis mucosae. Gastric and duodenal ulcer The prevalence of peptic ulcer (0.1–0.2%) is decreasing in many Western communities as a result of widespread use of Helicobacter pylori eradication therapy but it remains high in developing countries. The male-to-female ratio for duodenal ulcer varies from 5 : 1 to 2 : 1, while that for gastric ulcer is 2 : 1 or less. Chronic gastric ulcer is usually single; 90% are situated on the lesser curve within the antrum or at the junction between body and antral mucosa. Chronic duodenal ulcer usually occurs in the first part of the duodenum and 50% are on the anterior wall. Gastric and duodenal ulcers coexist in 10% of patients and more than one peptic ulcer is found in 10–15% of patients. Pathophysiology H. pylori Peptic ulceration is strongly associated with H. pylori infection. The prevalence of the infection in developed nations rises with age and Fig. 21.35 Factors that influence the virulence of Helicobacter pylori. Flagella Urease Urea H2O 2CO2 NH3 Ammonia 'cloud' Other factors • Vacuolating cytotoxin (vacA) • Cytotoxin-associated gene (cagA) • Adhesins (babA) • Outer inflammatory protein A (oipA) Type IV secretion system 21.33 Common causes of gastritis Acute gastritis (often erosive and haemorrhagic) • Aspirin, NSAIDs • Helicobacter pylori (initial infection) • Alcohol • Other drugs, e.g. iron preparations • Severe physiological stress, e.g. burns, multi-organ failure, central nervous system trauma • Bile reflux, e.g. following gastric surgery • Viral infections, e.g. CMV, herpes simplex virus in HIV/AIDS (p. 316) Chronic non-specific gastritis • H. pylori infection • Autoimmune (pernicious anaemia) • Post-gastrectomy Chronic ‘specific’ forms (rare) • Infections, e.g. CMV, tuberculosis • Gastrointestinal diseases, e.g. Crohn’s disease • Systemic diseases, e.g. sarcoidosis, graft-versus-host disease • Idiopathic, e.g. granulomatous gastritis (CMV = cytomegalovirus; NSAIDs = non-steroidal anti-inflammatory drugs)

NSAIDs Treatment with NSAIDs is associated with peptic ulcers due to impairment of mucosal defences, as discussed on page 1002. Smoking Smoking confers an increased risk of gastric ulcer and, to a lesser extent, duodenal ulcer. Once the ulcer has formed, it is more likely to cause complications and less likely to heal if the patient continues to smoke. Clinical features Peptic ulcer disease is a chronic condition with spontaneous relapses and remissions lasting for decades, if not for life. The most common presentation is with recurrent abdominal pain that has three notable characteristics: localisation to the epigastrium, relationship to food and episodic occurrence. Occasional vomiting occurs in about 40% of ulcer subjects; persistent daily vomiting suggests gastric outlet obstruction. In one-third, the history is less characteristic, especially in elderly people or those taking NSAIDs. In this situation, pain may be absent or so slight that it is experienced only as a vague sense of epigastric unease. Occasionally, the only symptoms are anorexia and nausea, or early satiety after meals. In some patients, the ulcer is completely ‘silent’, presenting for the first time with anaemia from chronic undetected blood loss, as abrupt haematemesis or as acute perforation; in others, there is recurrent acute bleeding without ulcer pain. The diagnostic value of

individual symptoms for peptic ulcer disease is poor; the history is therefore a poor predictor of the presence of an ulcer. Investigations Endoscopy is the preferred investigation (Fig. 21.38). Gastric ulcers may occasionally be malignant and therefore must always be biopsied and followed up to ensure healing. Patients should be tested for H. pylori infection. The current options available are listed in Box 21.34. Some are invasive and require endoscopy; others are non-invasive. They vary in sensitivity and specificity. Breath tests or faecal antigen tests are best because of accuracy, simplicity and non-invasiveness. to 10% in the West), the infection causes an antral-predominant pattern of gastritis characterised by hypergastrinaemia and a very exaggerated acid production by parietal cells, which could lead to duodenal ulceration (Fig. 21.36). In a much smaller number of infected people, H. pylori causes a corpus-predominant pattern of gastritis leading to gastric atrophy and hypochlorhydria. This phenotype is much more common in Asian countries, particularly Japan, China and Korea. The hypochlorhydria allows other bacteria to proliferate within the stomach; these other bacteria continue to drive the chronic inflammation and produce mutagenic nitrites from dietary nitrates, predisposing to the development of gastric cancer (Fig. 21.37). The effects of H. pylori are more complex in gastric ulcer patients compared to those with duodenal ulcers. The ulcer probably arises because of impaired mucosal defence resulting from a combination of H. pylori infection, NSAIDs and smoking, rather than excess acid. Fig. 21.36 Sequence of events in the pathophysiology of duodenal ulceration. G D

HCl Further inflammation and eventual ulceration Depletion of antral D-cell somatostatin Increased gastrin release from G cells Increased acid load in duodenum leads to gastric metaplasia Increased acid secretion Fig. 21.37 Consequences of Helicobacter pylori infection. (CagA = cytotoxin-associated gene; IL-1β = interleukin-1 beta; NSAIDs = non-steroidal anti-inflammatory drugs; TNF-α = tumour necrosis factor alpha; VacA = vacuolating cytotoxin) Host factors (IL-1β and TNF-α polymorphisms) Other environmental factors (NSAIDs, smoking) Helicobacter pylori factors (VacA, CagA) Gastric ulcer Duodenal ulcer Gastric cancer Antral gastritis Pangastritis Fig. 21.38 Endoscopic identification of a duodenal ulcer. The ulcer has a clean base and there are no stigmata of recent haemorrhage.

 first undergo eradication therapy to reduce ulcer risk. Subsequent co-prescription of a PPI along with the NSAID is advised but is not always necessary for patients being given low-dose aspirin, in whom the risk of ulcer complications is lower. Other indications for H. pylori eradication are shown in Box 21.36. Eradication of the infection has proven benefits in several extragastric disorders, including unexplained B12 deficiency and iron deficiency anaemia, once sources of gastrointestinal bleeding have been looked for and excluded. Platelet counts improve and may normalise after eradication therapy in patients with idiopathic thrombocytopenic purpura (p. 979); the mechanism for this is unclear. General measures Cigarette smoking, aspirin and NSAIDs should be avoided. Alcohol in moderation is not harmful and no special dietary advice is required. Maintenance treatment Continuous maintenance treatment should not be necessary after successful H. pylori eradication. For the minority who do require it, the lowest effective dose of PPI should be used. Surgical treatment Surgery is now rarely required for peptic ulcer disease but it is needed in some cases (Box 21.37). The operation of choice for a chronic non-healing gastric ulcer is partial gastrectomy, preferably with a Billroth I anastomosis, in which the ulcer itself and the ulcer-bearing area of the stomach are resected. The reason for this is to exclude an underlying Management The aims of management are to relieve symptoms, induce healing and prevent recurrence. H. pylori eradication is the cornerstone of therapy for peptic ulcers, as this will

successfully prevent relapse and eliminate the need for long-term therapy in the majority of patients. H. pylori eradication All patients with proven ulcers who are H. pylori-positive should be offered eradication as primary therapy. Treatment is based on a PPI taken simultaneously with two antibiotics (from amoxicillin, clarithromycin and metronidazole) for at least 7 days. High-dose, twice-daily PPI therapy increases efficacy of treatment, as does extending treatment to 10–14 days. Success is achieved in 80–90% of patients, although adherence, side-effects (Box 21.35) and antibiotic resistance influence this. Resistance to amoxicillin is rare but rates of metronidazole resistance reach more than 50% in some countries and rates of clarithromycin resistance of 20–40% have recently become common. Where the latter exceed 15%, a quadruple therapy regimen, consisting of omeprazole (or another PPI), bismuth subcitrate, metronidazole and tetracycline (OBMT) for 10–14 days, is recommended. In areas of low clarithromycin resistance, this regimen should also be offered as second-line therapy to those who remain infected after initial therapy, once adherence has been checked. For those who are still colonised after two treatments, the choice lies between a third attempt guided by antimicrobial sensitivity testing, rescue therapy (levofloxacin, PPI and clarithromycin) or long-term acid suppression. H. pylori and NSAIDs are independent risk factors for ulcer disease and patients requiring long-term NSAID therapy should 21.35 Common side-effects of Helicobacter pylori eradication therapy • Diarrhoea: 30–50% of patients; usually mild but Clostridium difficile-associated diarrhoea can occur • Flushing and vomiting when taken with alcohol (metronidazole) • Nausea, vomiting • Abdominal cramps • Headache • Rash 21.34 Methods for the diagnosis of Helicobacter pylori infection Test Advantages Disadvantages Non-invasive Serology Rapid office kits available Good for population studies Lacks specificity Cannot differentiate current from past infection 13C-urea breath test High sensitivity and specificity Requires expensive mass spectrometer Faecal antigen test Cheap, specific (> 95%) Acceptability Invasive (antral biopsy) Histology Specificity False negatives Takes several days to process Rapid urease test Cheap, quick, specific (> 95%) Sensitivity 85% Microbiological culture ‘Gold standard’ Defines antibiotic sensitivity Slow and laborious Lacks sensitivity 21.36 Indications for Helicobacter pylori eradication Definite • Peptic ulcer • Extranodal marginal-zone lymphomas of MALT type • Family history of gastric cancer • Previous resection for gastric cancer • H. pylori-positive dyspepsia • Long-term NSAID or low-dose aspirin users • Chronic (> 1 year) PPI users • Extragastric disorders: Unexplained vitamin B12 deficiency* Idiopathic thrombocytopenic purpura* Iron deficiency anaemia* (see text) Not indicated • Gastro-oesophageal reflux disease • Asymptomatic people without gastric cancer risk factors (MALT = mucosa-associated lymphoid tissue; NSAID = non-steroidal anti-inflammatory drug; PPI = proton pump inhibitor) *If H. pylori-positive on testing. 21.37 Indications for surgery in peptic ulcer Emergency • Perforation • Haemorrhage Elective • Gastric outflow obstruction • Persistent ulceration despite adequate medical therapy • Recurrent ulcer following gastric surgery

independent risk factor for late development of malignancy in the gastric remnant but the risk is higher in those with hypochlorhydria, duodenogastric reflux of bile, smoking and H. pylori infection. Although the relative risk is increased, the absolute risk of cancer remains low and endoscopic surveillance is not indicated following gastric surgery. Complications of peptic ulcer disease Perforation When perforation occurs, the contents of the stomach escape into the peritoneal cavity, leading to peritonitis. This is more common in duodenal than in gastric ulcers and is usually found with ulcers on the anterior wall. About one-quarter of all perforations occur in acute ulcers and

NSAIDs are often incriminated. Perforation can be the first sign of ulcer and a history of recurrent epigastric pain is uncommon. The most striking symptom is sudden, severe pain; its distribution follows the spread of the gastric contents over the peritoneum. The pain initially develops in the upper abdomen and rapidly becomes generalised; shoulder tip pain is caused by irritation of the diaphragm. The pain is accompanied by shallow respiration, due to limitation of diaphragmatic movements, and by shock. The abdomen is held immobile and there is generalised ‘board-like’ rigidity. Bowel sounds are absent and liver dullness to percussion decreases due to the presence of gas under the diaphragm. After some hours, symptoms may improve, although abdominal rigidity remains. Later, the patient’s condition deteriorates as general peritonitis develops. In at least 50% of cases, an erect chest X-ray shows free air beneath the diaphragm (see Fig. 21.11B, p. 773). If not, a water-soluble contrast swallow will confirm leakage of gastroduodenal contents. After resuscitation, the acute perforation should be treated surgically, either by simple closure or by conversion of the perforation into a pyloroplasty if it is large. On rare occasions, a ‘Polya’ partial gastrectomy is required. Following surgery, H. pylori should be treated (if present) and NSAIDs avoided. Perforation carries a mortality of 25%, reflecting the advanced age and significant comorbidity of the population that are affected. Gastric outlet obstruction The causes are shown in Box 21.39. The most common is an ulcer in the region of the pylorus. The presentation is with nausea, vomiting and abdominal distension. Large quantities of gastric content are often vomited and food eaten 24 hours or more previously may be recognised. Physical examination may show evidence of wasting and dehydration. A succussion splash may be elicited 4 hours or more after the last meal or drink. Visible gastric peristalsis is diagnostic of gastric outlet obstruction. Loss of acidic gastric contents leads to alkalosis and dehydration with low serum chloride and potassium and raised serum bicarbonate and urea concentrations (hypochloraemic metabolic alkalosis). cancer. In an emergency, ‘under-running’ the ulcer for bleeding or ‘oversewing’ (patch repair) for perforation is all that is required, in addition to taking a biopsy. For giant duodenal ulcers, partial gastrectomy using a ‘Polya’ or Billroth II reconstruction may be required. Complications of gastric resection or vagotomy Up to 50% of patients who undergo gastric surgery for peptic ulcer surgery experience long-term adverse effects. In most cases these are minor but in 10% they significantly impair quality of life. Dumping Rapid gastric emptying leads to distension of the proximal small intestine as the hypertonic contents draw fluid into the lumen. This leads to abdominal discomfort and diarrhoea after eating. Autonomic reflexes release a range of gastrointestinal hormones that provoke vasomotor features, such as flushing, palpitations, sweating, tachycardia and hypotension. Patients should therefore avoid large meals with high carbohydrate content. Chemical (bile reflux) gastropathy Duodenogastric bile reflux leads to chronic gastropathy. Treatment with aluminium-containing antacids or sucralfate may be effective. A few patients require revisional surgery with creation of a Roux en Y loop to prevent bile reflux. Diarrhoea and maldigestion Diarrhoea may develop after any peptic ulcer operation and usually occurs 1–2 hours after eating. Poor mixing of food in the stomach, with rapid emptying, inadequate mixing with pancreaticobiliary secretions, rapid transit and bacterial overgrowth, may lead to malabsorption. Diarrhoea often responds to small, dry meals with a reduced intake of refined carbohydrates. Antidiarrhoeal drugs, such as codeine phosphate (15–30 mg 4–6 times daily) or loperamide (2 mg after each loose stool), are helpful. Weight loss Most patients lose weight shortly after surgery and 30–40% are unable to regain all the weight that is lost. The usual cause is reduced intake because of a small gastric remnant but diarrhoea and mild steatorrhoea also contribute. Anaemia Anaemia is common many years after subtotal gastrectomy. Iron deficiency is the most common cause; folic acid and B12 deficiency are much less frequent. Inadequate dietary intake of iron and folate, lack of acid and

intrinsic factor secretion, mild chronic low-grade blood loss from the gastric remnant and recurrent ulceration are responsible. Metabolic bone disease Both osteoporosis and osteomalacia can occur as a consequence of calcium and vitamin D malabsorption. Gastric cancer An increased risk of gastric cancer has been reported from several epidemiological studies. Surgery itself is an 21.38 Peptic ulcer disease in old age • Gastroduodenal ulcers: have a greater incidence, admission rate and mortality. • Causes: high prevalence of H. pylori, use of non-steroidal anti-inflammatory drugs and impaired defence mechanisms. • Atypical presentations: pain and dyspepsia are frequently absent or atypical. Older people often develop complications, such as bleeding or perforation, without a dyspeptic history. • Bleeding: older patients require more intensive management because they have more limited reserve to withstand hypovolaemia. 21.39 Differential diagnosis and management of gastric outlet obstruction Cause Management Fibrotic stricture from duodenal ulcer (pyloric stenosis) Balloon dilatation or surgery Oedema from pyloric channel or duodenal ulcer Proton pump inhibitor therapy Carcinoma of antrum Surgery Adult hypertrophic pyloric stenosis Surgery

802 • GASTROENTEROLOGY of MEN 1). Some patients present with metastatic disease and, in these circumstances, surgery is inappropriate. In the majority of these individuals, continuous therapy with omeprazole or other PPIs can be successful in healing ulcers and alleviating diarrhoea, although double the normal dose is required. The synthetic somatostatin analogue, octreotide, given by subcutaneous injection, reduces gastrin secretion and may be of value. Other treatment options for pancreatic neuro-endocrine tumours are discussed on page 678. Overall 5-year survival is 60–75% and all patients should undergo genetic screening for MEN 1. Functional disorders Functional dyspepsia This is defined as chronic dyspepsia in the absence of organic disease. Other commonly reported symptoms include early satiety, fullness, bloating and nausea. ‘Ulcer-like’ and ‘dysmotility-type’ subgroups are often reported but there is overlap between these and with irritable bowel syndrome. Pathophysiology The cause is poorly understood but probably covers a spectrum of mucosal, motility and psychiatric disorders. Clinical features Patients are usually young (< 40 years) and women are affected twice as commonly as men. Abdominal discomfort is associated with a combination of other ‘dyspeptic’ symptoms, the most common being nausea, satiety and bloating after meals. Morning symptoms are characteristic and pain or nausea may occur on waking. Direct enquiry may elicit symptoms suggestive of irritable bowel syndrome. Peptic ulcer disease must be considered, while in older people intra-abdominal malignancy is a prime concern. There are no diagnostic signs, apart from inappropriate tenderness on abdominal palpation, perhaps. Symptoms may appear disproportionate to clinical well-being and there is no weight loss. Patients often appear anxious. A drug history should be taken and the possibility of a depressive illness should be considered. Pregnancy should be ruled out in young women before radiological studies are undertaken. Alcohol misuse should be suspected when early-morning nausea and retching are prominent. Investigations The history will often suggest the diagnosis. All patients should be checked for H. pylori infection and patients over the age of 55 years should undergo endoscopy to exclude mucosal disease. While an ultrasound scan may detect gallstones, these are rarely responsible for dyspeptic symptoms. Management The most important elements are explanation and reassurance. Possible psychological factors should be explored and the concept of psychological influences on gut function should be explained. Idiosyncratic and restrictive diets are of little benefit but smaller portions and fat restriction may help. Up to 10% of patients benefit from H. pylori eradication therapy and this should be offered to infected individuals. Eradication also removes a major risk factor for peptic ulcers and gastric cancer but at

the cost of a small risk of side-effects and worsening symptoms of underlying gastro-oesophageal reflux disease. Drug treatment is not especially successful but merits trial. Antacids, Paradoxical aciduria occurs because of enhanced renal absorption of Na+ in exchange for H+. Endoscopy should be performed after the stomach has been emptied using a wide-bore nasogastric tube. Intravenous correction of dehydration is undertaken and, in severe cases, at least 4 L of isotonic saline and 80 mmol of potassium may be necessary during the first 24 hours. In some patients, PPI drugs heal ulcers, relieve pyloric oedema and overcome the need for surgery. Endoscopic balloon dilatation of benign stenoses may be possible in some patients but in others partial gastrectomy is necessary; this is best done after a 7-day period of nasogastric aspiration, which enables the stomach to return to normal size. A gastroenterostomy is an alternative operation but, unless this is accompanied by vagotomy, patients will require long-term PPI therapy to prevent stomal ulceration. Bleeding See page 780. Zollinger–Ellison syndrome This is a rare disorder characterised by the triad of severe peptic ulceration, gastric acid hypersecretion and a neuro-endocrine tumour (p. 678) of the pancreas or duodenum (‘gastrinoma’). It probably accounts for about 0.1% of all cases of duodenal ulceration. The syndrome occurs in either sex at any age, although it is most common between 30 and 50 years of age. Pathophysiology The tumour secretes gastrin, which stimulates acid secretion to its maximal capacity and increases the parietal cell mass three- to sixfold. The acid output may be so great that it reaches the upper small intestine, reducing the luminal pH to 2 or less. Pancreatic lipase is inactivated and bile acids are precipitated. Diarrhoea and steatorrhoea result. Around 90% of tumours occur in the pancreatic head or proximal duodenal wall. At least half are multiple and tumour size can vary from 1 mm to 20 cm. Approximately one-half to two-thirds are malignant but are often slow-growing. Between 20% and 60% of patients have multiple endocrine neoplasia (MEN) type 1 (p. 688). Clinical features The presentation is with severe and often multiple peptic ulcers in unusual sites, such as the post-bulbar duodenum, jejunum or oesophagus. There is a poor response to standard ulcer therapy. The history is usually short, and bleeding and perforations are common. Diarrhoea is seen in one-third or more of patients and can be the presenting feature. Investigations Hypersecretion of acid under basal conditions, with little increase following pentagastrin, may be confirmed by gastric aspiration. Serum gastrin levels are grossly elevated (10- to 1000-fold). Injection of the hormone secretin normally causes no change or a slight decrease in circulating gastrin concentrations, but in Zollinger–Ellison syndrome it produces a paradoxical and dramatic increase in gastrin. Tumour localisation (and staging) is best achieved by a combination of CT and EUS; radio-labelled somatostatin receptor scintigraphy and 68gallium DOTATATE PET scanning may also be used for tumour detection and staging. Management Some 30% of small and single tumours can be localised and resected but many tumours are multifocal (especially in the context

after 50 years of age. Studies of Japanese migrants to the USA have revealed a much lower incidence in the second generation, confirming the importance of environmental factors. The overall prognosis is poor, with less than 30% surviving 5 years, and the best hope for improved survival lies in more efficient detection of tumours at an earlier stage. Pathophysiology Infection with H. pylori plays a key pathogenic role and the infection has been classified by the International Agency for Research on Cancer (IARC) as a definite human carcinogen. It is associated with chronic atrophic gastritis, gastric mucosal atrophy and gastric cancer (Fig. 21.39). It has been estimated that H. pylori infection may contribute to the occurrence of gastric cancer in 70% of cases.

Although the majority of H. pylori-infected individuals have normal or increased acid secretion, a few become hypo- or achlorhydric and these people are thought to be at greatest risk. H. pylori-induced chronic inflammation with generation of reactive oxygen species and depletion of the normally abundant antioxidant ascorbic acid are also important. There is strong evidence that H. pylori eradication, especially if achieved before irreversible pre-neoplastic changes (atrophy and intestinal metaplasia) have developed, reduces the risk of cancer development in high-risk populations and is cost-effective. Diets rich in salted, smoked or pickled foods and the consumption of nitrites and nitrates may increase cancer risk. Carcinogenic N-nitroso-compounds are formed from nitrates by the action of nitrite-reducing bacteria that colonise the achlorhydric stomach. Diets lacking in fresh fruit and vegetables, as well as vitamins C and A, may also contribute. Other risk factors are listed in Box 21.40. No predominant genetic abnormality has been identified, although cancer risk is increased two- to threefold in first-degree relatives of patients, and links with blood group A have been reported. Some host genetic factors related to inflammatory genes and prostate stem cell antigen have recently been associated with increased risk of gastric caner. Rarely, gastric cancer may be inherited in an autosomal dominant manner in association with mutations of the E-cadherin (CDH1) gene. such as hydrotalcite, are sometimes helpful. Prokinetic drugs, such as metoclopramide (10 mg 3 times daily) or domperidone (10–20 mg 3 times daily), may be given before meals if nausea, vomiting or bloating is prominent. Metoclopramide may induce extrapyramidal side-effects, including tardive dyskinesia in young patients. H2-receptor antagonist drugs may be tried if night pain or heartburn is troublesome. Low-dose tricyclic agents, such as amitriptyline, are of value in up to two-thirds. Symptoms that can be associated with an identifiable cause of stress resolve with appropriate counselling. Some patients have major psychological disorders that result in persistent or recurrent symptoms and need behavioural or other formal psychotherapy (p. 1190). Functional causes of vomiting Psychogenic retching or vomiting may arise in anxiety. It typically occurs on wakening or immediately after breakfast, and only rarely later in the day. The disorder is probably a reaction to facing up to the worries of everyday life; in the young, it can be due to school phobia. Early morning vomiting also occurs in pregnancy, alcohol misuse and depression. Although functional vomiting may occur regularly over long periods, there is little or no weight loss. Children, and less often adults, sometimes suffer from acute and recurrent disabling bouts of vomiting for days at a time. The cause of this cyclical vomiting syndrome is unknown but in some adults it is associated with cannabis use. In all patients it is essential to exclude other common causes (p. 780). Tranquillisers and antiemetic drugs (metoclopramide 10 mg 3 times daily, domperidone 10 mg 3 times daily, prochlorperazine 5–10 mg 3 times daily) have only a secondary place in management. Antidepressants in full dose may be effective (p. 1199). Gastroparesis Defective gastric emptying without mechanical obstruction of the stomach or duodenum can occur as a primary event, due to inherited or acquired disorders of the gastric pacemaker, or can be secondary to disorders of autonomic nerves (particularly diabetic neuropathy) or the gastroduodenal musculature (systemic sclerosis, myotonic dystrophies and amyloidosis). Drugs such as opiates, calcium channel antagonists and those with anticholinergic activity (tricyclics, phenothiazines) can also cause gastroparesis. Early satiety and recurrent vomiting are the major symptoms; abdominal fullness and a succussion splash may be present on examination. Treatment is based on small, frequent, low-fat meals and the use of metoclopramide and domperidone. In severe cases, nutritional failure can occur and long-term jejunostomy feeding or total parenteral nutrition is required. Surgical insertion of a gastric neurostimulator has been successful in some cases, especially those complicating diabetic autonomic neuropathy. Tumours of the stomach Gastric carcinoma Gastric carcinoma is the third leading cause of cancer death

worldwide but there is marked geographical variation in incidence. It is most common in China, Japan, Korea (incidence 40/100 000 males), Eastern Europe and parts of South America (20/100 000). Rates in the UK are 12/100 000 for men. In most countries, the incidence is 50% lower in women. In both sexes, it rises sharply Fig. 21.39 Gastric carcinogenesis: a possible mechanism. (CagA = cytotoxin-associated gene) Helicobacter pylori Diet Smoking Nitrosamines Dietary nitrates Helicobacter pylori CagA Carcinoma Normal gastric epithelium Chronic atrophic gastritis Intestinal metaplasia Dysplasia Bacterial colonisation of stomach Achlorhydria

804 • GASTROENTEROLOGY made, further imaging is necessary for staging and assessment of resectability. CT will provide evidence of intra-abdominal spread or liver metastases. Even with these techniques, laparoscopy with peritoneal washings is required to determine whether the tumour is resectable, as it is the only modality that will reliably detect peritoneal spread. Management Surgery Resection offers the only hope of cure and this can be achieved in about 90% of patients with early gastric cancer. For the majority of patients with locally advanced disease, total gastrectomy with lymphadenectomy is the operation of choice, preserving the spleen if possible. Proximal tumours involving the oesophagogastric junction also require a distal oesophagectomy. Small, distally sited tumours can be managed by a partial gastrectomy with lymphadenectomy and either a Billroth I or a Roux en Y reconstruction. More extensive lymph node resection may increase survival rates but carries greater morbidity. Even for those who cannot be cured, palliative resection may be necessary when patients present with bleeding or gastric outflow obstruction. Following surgery, recurrence is much more likely if serosal penetration has occurred, although complete removal of all macroscopic tumour combined with lymphadenectomy will achieve a 50–60% 5-year survival. Perioperative chemotherapy with epirubicin, cisplatin and fluorouracil (ECF) improves survival rates. Palliative treatment In patients with inoperable tumours, survival can be improved and palliation of symptoms achieved with chemotherapy using 5-fluorouracil and cisplatin, ECF or other platinum- and taxanebased regimens. The biological agent trastuzumab may benefit some patients whose tumours over-express HER2 (p. 1322). Endoscopic laser ablation for control of dysphagia or recurrent bleeding benefits some patients. Carcinomas at the cardia or pylorus may require endoscopic dilatation or insertion of expandable metallic stents for relief of dysphagia or vomiting. A nasogastric tube may offer temporary relief of vomiting due to gastric outlet obstruction (Box 21.41). Virtually all tumours are adenocarcinomas arising from mucussecreting cells in the base of the gastric crypts. Most develop on a background of chronic atrophic gastritis with intestinal metaplasia and dysplasia. Cancers are either ‘intestinal’, arising from areas of intestinal metaplasia with histological features reminiscent of intestinal epithelium, or ‘diffuse’, arising from normal gastric mucosa. Intestinal carcinomas are more common and arise against a background of chronic mucosal injury. Diffuse cancers tend to be poorly differentiated and occur in younger patients. In the developing world, 50% of gastric cancers develop in the antrum; 20–30% occur in the gastric body, often on the greater curve; and 20% are found in the cardia. In Western populations, however, proximal gastric tumours are becoming more common than those arising in the body and distal stomach. This change in disease pattern may be a reflection of changes in lifestyle or the decreasing prevalence of H. pylori in the West. Diffuse submucosal infiltration by a scirrhous cancer (linitis plastica) is uncommon. Early gastric cancer is defined as cancer confined to the mucosa or submucosa. It is more often recognised in Japan, where widespread screening is practised. Some cases can be cured by endoscopic mucosal or submucosal resection. The majority of patients (> 80%) in the West, however, present with advanced gastric cancer. Clinical features Early gastric cancer is usually asymptomatic but may be

discovered during endoscopy for investigation of dyspepsia. Two-thirds of patients with advanced cancers have weight loss and 50% have ulcer-like pain. Anorexia and nausea occur in one-third, while early satiety, haematemesis, melaena and dyspepsia alone are less common. Dysphagia occurs in tumours of the gastric cardia that obstruct the gastro-oesophageal junction. Anaemia from occult bleeding is also common. Examination may reveal no abnormalities but signs of weight loss, anaemia and a palpable epigastric mass are not infrequent. Jaundice or ascites signifies metastatic spread. Occasionally, tumour spread occurs to the supraclavicular lymph nodes (Troisier's sign), umbilicus (Sister Joseph's nodule) or ovaries (Krukenberg tumour). Paraneoplastic phenomena, such as acanthosis nigricans, thrombophlebitis (Trousseau's sign) and dermatomyositis, occur rarely. Metastases arise most commonly in the liver, lungs, peritoneum and bone marrow. Investigations Upper gastrointestinal endoscopy is the investigation of choice (Fig. 21.40) and should be performed promptly in any dyspeptic patient with 'alarm features' (see Box 21.15, p. 779). Multiple biopsies from the edge and base of a gastric ulcer are required. Barium meal is a poor alternative, since any abnormalities must be followed by endoscopy and biopsy. Once the diagnosis is 21.40 Risk factors for gastric cancer • Helicobacter pylori • Smoking • Alcohol • Dietary associations (see text) • Autoimmune gastritis (pernicious anaemia) • Adenomatous gastric polyps • Previous partial gastrectomy (> 20 years) • Ménétrier's disease • Hereditary diffuse gastric cancer families (CDH1 mutations) • Familial adenomatous polyposis (p. 828) Fig. 21.40 Gastric carcinoma. Endoscopic finding of a large polypoidal mass arising from the wall of the stomach.

prognosis are stage I or II disease, small resectable tumours, tumours with low-grade histology, and age below 60 years. Other tumours of the stomach Gastrointestinal stromal cell tumours (GISTs), arising from the interstitial cells of Cajal, are occasionally found at upper gastrointestinal endoscopy. They are differentiated from other mesenchymal tumours by expression of the c-kit proto-oncogene, which encodes a tyrosine kinase receptor. These tumours, particularly the smaller lesions of less than 2 cm, are usually benign and asymptomatic, but the larger ones may have malignant potential and may occasionally be responsible for dyspepsia, ulceration and gastrointestinal bleeding. Small lesions (< 2 cm) are usually followed by endoscopy, while larger ones require surgical resection. Very large lesions should be treated pre-operatively with imatinib (a tyrosine kinase inhibitor) to reduce their size and make surgery easier. Imatinib can also provide prolonged control of metastatic GISTs. A variety of polyps occur. Hyperplastic polyps and fundic cystic gland polyps are common and of no consequence. Adenomatous polyps are rare but have malignant potential and should be removed endoscopically. Occasionally, gastric carcinoid tumours are seen in the fundus and body in patients with long-standing pernicious anaemia. These benign tumours arise from ECL or other endocrine cells, and are often multiple but rarely invasive. Unlike carcinoid tumours arising elsewhere in the gastrointestinal tract, they usually run a benign and favourable course. Large (> 2 cm) carcinoids may, however, metastasise and should be removed. Rarely, small nodules of ectopic pancreatic exocrine tissue are found. These 'pancreatic rests' may be mistaken for gastric neoplasms and usually cause no symptoms. EUS is the most useful investigation. Diseases of the small intestine Disorders causing malabsorption Coeliac disease Coeliac disease is an inflammatory disorder of the small bowel occurring in genetically susceptible individuals, which results from intolerance to wheat gluten and similar proteins found in rye, barley and, to a lesser extent, oats. It can result in malabsorption and responds to a gluten-free diet. The

condition occurs worldwide but is more common in northern Europe. The prevalence in the UK is approximately 1%, although 50% of these people are asymptomatic. These include both undiagnosed ‘silent’ cases of the disease and cases of ‘latent’ coeliac disease – genetically susceptible people who may later develop clinical coeliac disease. Pathophysiology The precise mechanism of mucosal damage is unclear but immunological responses to gluten play a key role (Fig. 21.41). There is a strong genetic component, with around 10% of first-degree relatives of an index case affected, and there is strong (approximately 75%) concordance in monozygotic twins. There is a strong association with human leukocyte antigen (HLA)-DQ2/DQ8. Dysbiosis of the intestinal microbiota has been identified but it is unclear if this is pathological or a response to the underlying mucosal changes. Gastric lymphoma This is a rare tumour, accounting for less than 5% of all gastric malignancies. The stomach is, however, the most common site for extranodal non-Hodgkin lymphoma and 60% of all primary gastrointestinal lymphomas occur at this site. Lymphoid tissue is not found in the normal stomach but lymphoid aggregates develop in the presence of H. pylori infection. Indeed, H. pylori infection is closely associated with the development of a low-grade lymphoma (classified as extranodal marginal-zone lymphomas of MALT type). EUS plays an important role in staging these lesions by accurately defining the depth of invasion into the gastric wall. The clinical presentation is similar to that of gastric cancer and endoscopically the tumour appears as a polypoid or ulcerating mass. While initial treatment of low-grade lesions confined to the superficial layers of the gastric wall consists of H. pylori eradication and close observation, 25% contain t(11 : 18) chromosomal translocations. In these cases, additional radiotherapy or chemotherapy is usually necessary. High-grade B-cell lymphomas should be treated by a combination of rituximab, chemotherapy (p. 962), surgery and radiotherapy. The choice depends on the site and extent of tumour, the presence of comorbid illnesses, and other factors, such as symptoms of bleeding and gastric outflow obstruction. The prognosis depends on the stage at diagnosis. Features predicting a favourable 21.41 How to insert a nasogastric tube Equipment • 8–9F ‘fine-bore’ tube for feeding or 16–18F ‘wide-bore’ tube for drainage • Lubricant jelly • Cup of water and straw for sipping • Adhesive tape • pH (not litmus) paper • Sickness bowl and tissues • Catheter drainage bag and clamp (for drainage) Technique • A clear explanation and a calm patient are essential • Establish a ‘stop signal’ for the patient to use, if needed • Ask the patient to sit semi-upright • Examine the nose for deformity or blockage to determine which side to use • Measure the distance from ear to xiphoid process via the nose and mark the position on the tube • Advance the lubricated tube tip slowly along the floor of the nasal passage to the oropharynx • Ask the patient to sip water and advance the tube 2–3 cm with each swallow • Stop, withdraw and retry if the patient is distressed or coughing, as the tube may have entered the larynx • Advance until the mark on the tube reaches the tip of the nose and secure with tape • Aspirate the contents and check pH (gastric acid confirmed if pH < 5). If in doubt, perform a chest X-ray to confirm tube position (usually necessary with feeding tubes) • Attach the catheter drainage bag, if necessary, and clamp Aftercare • Flush the tube daily after feeding or drug dosing • Check position regularly and look for signs of displacement • Check with the pharmacist what drugs, if any, can be safely given via the tube

 usually characteristic but other causes of villous atrophy should be considered (Box 21.43 and Fig. 21.42). Sometimes the villi appear normal but there are excess numbers of intra-epithelial lymphocytes (lymphocytic duodenosis). Antibodies Antibody tests constitute a valuable screening tool in patients with diarrhoea or other suggestive symptoms but are not a diagnostic substitute for small bowel biopsy at present. Tissue transglutaminase (tTG) is

now recognised as the autoantigen for Fig. 21.41 Pathophysiology of coeliac disease. After being taken up by epithelial cells, gluten peptides are deamidated by the enzyme tissue transglutaminase in the subepithelial layer. They are then able to fit the antigen-binding motif on human leucocyte antigen (HLA)-DQ2-positive antigenpresenting cells. Recognition by CD4+ T cells triggers a Th1 immune response with generation of pro-inflammatory cytokines: interleukin-1 (IL-1), interferon gamma (IFN-γ) and tumour necrosis factor alpha (TNF-α). Lymphocytes infiltrate the lamina propria and an increase in intra-epithelial lymphocytes (IELs), crypt hyperplasia and villous atrophy ensue. Antigenpresenting cell CD4+ T cell HLA-DQ2 Deamidation Th1 response • IL-1 • IFN-γ • TNF-α Lumen Brush border Epithelium Tissue transglutaminase Gluten peptides IEL IEL Clinical features Coeliac disease can present at any age. In infancy, it occurs after weaning on to cereals and typically presents with diarrhoea, malabsorption and failure to thrive. In older children, it may present with non-specific features, such as delayed growth. Features of malnutrition are found on examination and mild abdominal distension may be present. Affected children have growth and pubertal delay, leading to short stature in adulthood. In adults, the disease usually presents during the third or fourth decade and females are affected twice as often as males. The presentation is highly variable, depending on the severity and extent of small bowel involvement. Some have florid malabsorption, while others develop non-specific symptoms, such as tiredness, weight loss, folate deficiency or iron deficiency anaemia. Other presentations include oral ulceration, dyspepsia and bloating. Unrecognised coeliac disease is associated with mild under-nutrition and osteoporosis. Coeliac disease is associated with other HLA-linked autoimmune disorders and with certain other diseases (Box 21.42). In some centres, people at higher risk of developing coeliac disease, such as those with type 1 diabetes, may undergo periodic antibody screening. Such screening may identify people with asymptomatic or minimally symptomatic disease; there is controversy about the optimum management strategy for such individuals. Investigations These are performed to confirm the diagnosis and to look for consequences of malabsorption. Duodenal biopsy Endoscopic small bowel biopsy is the gold standard. Endoscopic appearances should not preclude biopsy, as the mucosa usually looks normal. As the histological changes can be patchy, an adequate number of biopsies – currently, more than four biopsies from the second part of the duodenum plus one from the duodenal bulb – should be retrieved. The histological features are 21.43 Important causes of subtotal villous atrophy • Coeliac disease • Tropical sprue • Dermatitis herpetiformis • Lymphoma • HIV-related enteropathy • Giardiasis • Hypogammaglobulinaemia • Radiation • Whipple’s disease • Zollinger–Ellison syndrome 21.42 Disease associations of coeliac disease • Type 1 diabetes mellitus (2–8%) • Thyroid disease (5%) • Primary biliary cirrhosis (3%) • Sjögren’s syndrome (3%) • Immunoglobulin A deficiency (2%) • Pernicious anaemia • Sarcoidosis • Neurological complications: Encephalopathy Cerebellar atrophy Peripheral neuropathy Epilepsy • Myasthenia gravis • Dermatitis herpetiformis • Down’s syndrome • Enteropathy-associated T-cell lymphoma • Small bowel carcinoma • Squamous carcinoma of oesophagus • Ulcerative jejunitis • Pancreatic insufficiency • Microscopic colitis • Splenic atrophy

circumstances, if the diet is satisfactory, then other conditions, such as pancreatic insufficiency or microscopic colitis, should be sought, as should complications of coeliac disease, such as ulcerative jejunitis or enteropathy-associated T-cell lymphoma. There remain a small number of patients who fail to respond adequately to a gluten-free diet and they require therapy with glucocorticoids or immunosuppressive drugs. Complications A twofold-increased risk of malignancy, particularly of

enteropathyassociated T-cell lymphoma, small bowel carcinoma and squamous carcinoma of the oesophagus, has been reported. A few patients develop ulcerative jejuno-ileitis. This may present with fever, pain, obstruction or perforation. This diagnosis can be made by barium studies or enteroscopy but laparotomy and full-thickness biopsy may be required. Treatment is difficult. Glucocorticoids are used with mixed success and some patients require surgical resection and parenteral nutrition. The course is often progressive. Osteoporosis and osteomalacia may occur in patients with longstanding, poorly controlled coeliac disease. These complications are less common in those who adhere strictly to a gluten-free diet. Dermatitis herpetiformis This is characterised by crops of intensely itchy blisters over the elbows, knees, back and buttocks (p. 1256). Immunofluorescence shows granular or linear IgA deposition at the dermo-epidermal junction. Almost all patients have partial villous atrophy on duodenal biopsy, identical to that seen in coeliac disease, even though they usually have no gastrointestinal symptoms. In contrast, fewer than 10% of coeliac patients have evidence of dermatitis herpetiformis, although both disorders are associated with the same histocompatibility antigen groups. The rash usually responds to a gluten-free diet but some patients require additional treatment with dapsone (100–150 mg daily). Tropical sprue Tropical sprue is defined as chronic, progressive malabsorption in a patient in or from the tropics, associated with abnormalities of small intestinal structure and function. The disease occurs mainly in the West Indies and in southern India, Malaysia and Indonesia. Pathophysiology The epidemiological pattern and occasional epidemics suggest that an infective agent may be involved. Although no single bacterium has been isolated, the condition often begins after an acute diarrhoeal illness. Small bowel bacterial overgrowth with Escherichia coli, Enterobacter and Klebsiella is frequently seen. The changes closely resemble those of coeliac disease. anti-endomysial antibodies. If the antibody screen is positive, adult patients should remain on a gluten-containing diet until duodenal biopsies are taken. High-titre serology in children can be diagnostic without the need for endoscopy and biopsy. Antibody titres usually become negative with successful treatment. Anti-endomysial antibodies of the IgA class are detectable by immunofluorescence in most untreated cases. They are sensitive (85–95%) and specific (approximately 99%) for the diagnosis, except in very young infants. IgG antibodies, however, must be analysed in patients with coexisting IgA deficiency. The tTG assay has become the serological test of choice in many countries, as it is easier to perform, is semi-quantitative, has more than 95% sensitivity and specificity, and is more accurate in patients with IgA deficiency. Haematology and biochemistry A full blood count may show microcytic or macrocytic anaemia from iron or folate deficiency and features of hyposplenism (target cells, spherocytes and Howell–Jolly bodies). Biochemical tests may reveal reduced concentrations of calcium, magnesium, total protein, albumin or vitamin D. Serum IgA measurement is required to ensure an appropriate IgA response and to allow analysis of serological testing. Other investigations Measurement of bone density should be considered to look for evidence of osteoporosis, especially in older patients and post-menopausal women. Management The aims are to correct existing deficiencies of micronutrients, such as iron, folate, calcium and/or vitamin D, and to achieve mucosal healing through a life-long gluten-free diet. This requires the exclusion of wheat, rye, barley and initially oats, although oats may be re-introduced safely in most patients after 6–12 months. Initially, frequent dietary counselling is required to make sure the diet is being observed, as the most common reason for failure to improve with dietary treatment is accidental or unrecognised gluten ingestion. Mineral and vitamin supplements are also given when indicated but are seldom necessary when a strict gluten-free diet is adhered to. Booklets produced by coeliac societies in many countries, containing diet sheets and recipes for the use of gluten-free flour, are of great value. Dietetic follow-up is key

to management. Patients should be followed up after initiation of a gluten-free diet, with assessment of symptoms, weight and nutritional status, and blood should be taken for measurement of tTG or anti-endomysial antibodies. There are currently no additional non-invasive tests to assess small bowel mucosal healing. Repeat small bowel biopsies are not required routinely but should be considered in patients whose symptoms fail to improve and those in whom antibody levels remain high. In these Fig. 21.42 Jejunal mucosa. A Normal. B Subtotal villous atrophy in coeliac disease. There is blunting of villi (B), crypt hyperplasia (H) and inflammatory infiltration of the lamina propria (I). A B H B I

808 • GASTROENTEROLOGY hypogammaglobulinaemia (p. 78), bacterial overgrowth occurs because the IgA and IgM levels in serum and jejunal secretions are reduced. Chronic diarrhoea and malabsorption occur because of bacterial overgrowth and recurrent gastrointestinal infections (particularly giardiasis, p. 287). Clinical features The patient presents with watery diarrhoea and/or steatorrhoea, and with anaemia due to B12 deficiency. These arise because of deconjugation of bile acids, which impairs micelle formation, and because of bacterial utilisation of vitamin B12. There may also be symptoms from the underlying intestinal cause. Investigations The diagnosis of blind loops or fistulae can often be made by barium small bowel meal and follow-through or small bowel MRI enterography. Endoscopic duodenal biopsies are useful in excluding coeliac disease. Jejunal contents for bacteriological examination can also be aspirated at endoscopy but laboratory analysis requires anaerobic and aerobic culture techniques. Bacterial overgrowth can also be diagnosed non-invasively using hydrogen breath tests, although they lack sensitivity. These simple, non-radioactive tests involve serial measurement of breath samples for hydrogen after oral ingestion of 50 g of glucose or lactulose. If bacteria are present within the small bowel, they rapidly metabolise the glucose, causing an early rise in exhaled hydrogen, in advance of that normally resulting from metabolism by colonic flora. Biochemical analysis may reveal low serum levels of vitamin B12, with normal or elevated folate levels because the bacteria produce folic acid. Hypogammaglobulinaemia can be diagnosed by measurement of serum immunoglobulins and by intestinal biopsy, which shows reduced or absent plasma cells and nodular lymphoid hyperplasia. Management The underlying cause of small bowel bacterial overgrowth should be addressed, where possible. A course of broad-spectrum antibiotic for 2 weeks is the first-line treatment, although there is no consensus on agent or dose. Examples include tetracycline (250 mg 4 times daily), metronidazole (400 mg 3 times daily), amoxicillin (250 mg 3 times daily) or ciprofloxacin (250 mg twice daily). If breath testing reveals high methane production, addition of neomycin (500 mg twice daily) may be beneficial. Up to 50% of patients do not respond adequately and relapse rates are high. Some patients require up to 4 weeks of treatment and, in a few, continuous rotating courses of antibiotics are necessary. Consideration should be given to the risk of emerging antimicrobial resistance. Intramuscular vitamin B12 supplementation may be needed in chronic cases, as the bacteria utilise vitamin B12. Patients with motility disorders, such as diabetes and systemic sclerosis, can sometimes benefit from antidiarrhoeal drugs (diphenoxylate (5 mg 3 times daily orally) or loperamide (2 mg 4–6 times daily) orally). Giardiasis should Clinical features There is diarrhoea, abdominal distension, anorexia, fatigue and weight loss. In visitors to the tropics, the onset of severe diarrhoea may be sudden and accompanied by fever. When the disorder becomes chronic, the features of megaloblastic anaemia (vitamin B12 and folic acid malabsorption) and other deficiencies, including ankle oedema, glossitis and stomatitis, are common. Remissions and relapses may occur. The differential diagnosis in the indigenous tropical population is an infective cause of diarrhoea. The important differential diagnosis in visitors to the tropics is giardiasis (p.

287). Management Tetracycline (250 mg 4 times daily for 28 days) is the treatment of choice and brings about long-term remission or cure. In most patients, pharmacological doses of folic acid (5 mg daily) improve symptoms and jejunal morphology. In some cases, treatment must be prolonged before improvement occurs and occasionally patients must leave the tropics. Small bowel bacterial overgrowth (‘blind loop syndrome’) The normal duodenum and jejunum contain fewer than 104/mL organisms, which are usually derived from saliva. The count of coliform organisms never exceeds 103/mL. In bacterial overgrowth, there may be 108–1010/mL organisms, most of which are normally found only in the colon. Disorders that impair the normal physiological mechanisms controlling bacterial proliferation in the intestine predispose to bacterial overgrowth (Box 21.44). The most important are loss of gastric acidity, impaired intestinal motility and structural abnormalities that allow colonic bacteria to gain access to the small intestine or provide a secluded haven from the peristaltic stream. Pathophysiology Bacterial overgrowth can occur in patients with small bowel diverticuli. Another cause is diabetic autonomic neuropathy (p. 760), which reduces small bowel motility and affects enterocyte secretion. In systemic sclerosis, bacterial overgrowth arises because the circular and longitudinal layers of the intestinal muscle are fibrosed and motility is abnormal. In idiopathic 21.44 Causes of small bowel bacterial overgrowth Mechanism Examples Hypo- or achlorhydria Pernicious anaemia Partial gastrectomy Long-term proton pump inhibitor therapy Impaired intestinal motility Systemic sclerosis Diabetic autonomic neuropathy Chronic intestinal pseudo-obstruction Structural abnormalities Gastric surgery (blind loop after Billroth II operation) Jejunal diverticulosis Enterocolic fistulae* Extensive small bowel resection Strictures* Impaired immune function Hypogammaglobulinaemia *Most commonly caused by Crohn’s disease. 21.45 Malabsorption in old age • Coeliac disease: symptoms such as dyspepsia tend to be vague; only 25% present classically with diarrhoea and weight loss. Metabolic bone disease, folate or iron deficiency, coagulopathy and small bowel lymphoma are more common. • Small bowel bacterial overgrowth: more common due to atrophic gastritis, resulting in hypo- or achlorhydria, increased prevalence of jejunal diverticulosis and long-term adverse effects of gastric surgery for ulcer disease.

usually resolve quickly and biopsy changes revert to normal in a few weeks. Long-term follow-up is essential, as clinical relapse occurs in up to one-third of patients, often within the CNS; in this case, the same therapy is repeated or else treatment with doxycycline and hydroxychloroquine is necessary. Bile acid diarrhoea Bile acid diarrhoea can occur idiopathically (type 1), as a complication of small bowel resection, post cholecystectomy (type 2) or in association with other conditions such as microscopic colitis, chronic pancreatitis, coeliac disease, small intestinal bacterial overgrowth or diabetes mellitus. The population prevalence is estimated at around 1% and the disease is often under-diagnosed. It is now appreciated that many patients diagnosed with diarrhoeapredominant irritable bowel syndrome have evidence of bile acid diarrhoea. The most common scenario is in patients with Crohn’s disease who have undergone ileal resection, which can also lead to other malabsorptive manifestations (Fig. 21.43). Unabsorbed bile salts pass into the colon, stimulating water and electrolyte secretion and causing diarrhoea. If hepatic synthesis of new bile acids cannot keep pace with faecal losses, fat malabsorption occurs. Another consequence is the formation of lithogenic bile, leading to gallstones. Renal calculi, rich in oxalate, develop. Normally, oxalate in the colon is bound to and precipitated by calcium. Unabsorbed bile salts preferentially bind calcium, leaving oxalate to be absorbed, with development of urinary oxalate

calculi. Patients have urgent watery diarrhoea or mild steatorrhoea. Contrast studies and tests of B12 and bile acid absorption, such as the 75Se-homocholic acid taurine (SeHCAT) test (p. 777), are useful investigations but are not available throughout the world due to use of synthetic radio-labelled compound. An elevated serum 7α-hydroxycholestenone is a useful non-invasive marker of bile acid diarrhoea. Diarrhoea usually responds well to bile acid sequestrants, such as colestyramine or colesevelam, which bind bile salts in the intestinal lumen. Aluminium hydroxide can be used as an alternative. Short bowel syndrome This is discussed in detail on page 708. Radiation enteritis and proctocolitis Intestinal damage occurs in 10–15% of patients undergoing radiotherapy for abdominal or pelvic malignancy. The risk varies with total dose, dosing schedule and the use of concomitant chemotherapy. Pathophysiology The rectum, sigmoid colon and terminal ileum are most frequently involved. Radiation causes acute inflammation, shortening of villi, oedema and crypt abscess formation. These usually resolve completely but some patients develop an obliterative endarteritis affecting the endothelium of submucosal arterioles over 2–12 months. In the longer term, this can provoke a fibrotic reaction, leading to adhesions, ulceration, strictures, obstruction or fistula to adjacent organs. Clinical features In the acute phase, there is nausea, vomiting, cramping abdominal pain and diarrhoea. When the rectum and colon are involved, rectal mucus, bleeding and tenesmus occur. The chronic phase develops after 5–10 years in some patients and produces one or more of the problems listed in Box 21.47. be controlled in patients with hypogammaglobulinaemia using metronidazole or tinidazole, but if symptoms fail to respond adequately, immunoglobulin infusions may be required. Whipple’s disease This rare condition is characterised by infiltration of small intestinal mucosa by ‘foamy’ macrophages, which stain positive with periodic acid–Schiff (PAS) reagent. The disease is a multisystem one and almost any organ can be affected, sometimes long before gastrointestinal involvement becomes apparent (Box 21.46). Pathophysiology Whipple’s disease is caused by infection with the Gram-positive bacillus Tropheryma whipplei, which becomes resident within macrophages in the bowel mucosa. Villi are widened and flattened, containing densely packed macrophages in the lamina propria, which obstruct lymphatic drainage and cause fat malabsorption. Clinical features Middle-aged Caucasian men are most frequently affected and presentation depends on the pattern of organ involvement. Low-grade fever is common and most patients have joint symptoms to some degree, often as the first manifestation. Occasionally, neurological manifestations may predominate and CNS involvement is the most serious consequence. Investigations Diagnosis is made by the characteristic features on small bowel biopsy, with characterisation of the bacillus by polymerase chain reaction (PCR). Management Whipple’s disease is often fatal if untreated but responds well, at least initially, to intravenous ceftriaxone (2 g daily for 2 weeks), followed by oral co-trimoxazole for at least 1 year. Symptoms 21.46 Clinical features of Whipple’s disease Gastrointestinal (> 70%) • Diarrhoea (75%) • Steatorrhoea • Weight loss (90%) • Protein-losing enteropathy • Ascites • Hepatosplenomegaly (< 5%) Musculoskeletal (65%) • Seronegative large joint arthropathy • Sacroiliitis Cardiac (10%) • Pericarditis • Myocarditis • Endocarditis • Coronary arteritis Neurological (10–40%) • Apathy • Fits • Dementia • Myoclonus • Meningitis • Cranial nerve lesions Pulmonary (10–20%) • Chronic cough • Pleurisy • Pulmonary infiltrates Haematological (60%) • Anaemia • Lymphadenopathy Other (40%) • Fever • Pigmentation

 It leads to fat malabsorption and deficiency of fat-soluble vitamins. Jejunal biopsy reveals enterocytes distended with resynthesised triglyceride and normal villous morphology. Serum cholesterol and triglyceride levels are low. A number of other abnormalities occur in this syndrome, including acanthocytosis, retinitis pigmentosa and a progressive

neurological disorder with cerebellar and dorsal column signs. Symptoms may be improved by a low-fat diet supplemented with medium-chain triglycerides and vitamins A, D, E and K. Motility disorders Chronic intestinal pseudo-obstruction Small intestinal motility is disordered in conditions that affect the smooth muscle or nerves of the intestine. Many cases are ‘primary’ (idiopathic), while others are ‘secondary’ to a variety of disorders or drugs (Box 21.48). Clinical features There are recurrent episodes of nausea, vomiting, abdominal discomfort and distension, often worse after food. Alternating constipation and diarrhoea occur and weight loss results from malabsorption (due to bacterial overgrowth) and fear of eating. There may also be symptoms of dysmotility affecting other parts of the gastrointestinal tract, such as dysphagia, and features of bladder dysfunction in primary cases. Some patients develop severe abdominal pain for reasons that are poorly understood and this can be difficult to manage. Investigations The diagnosis is often delayed and a high index of suspicion is needed. Plain X-rays show distended loops of bowel and air–fluid levels but barium studies demonstrate no mechanical obstruction. Laparotomy is sometimes required to exclude obstruction and to obtain full-thickness biopsies of the intestine. Examination of biopsy material using specialised techniques, such as electron microscopy, and immunohistochemistry can diagnose the many Investigations In the acute phase, the rectal changes at sigmoidoscopy resemble ulcerative proctitis (see Fig. 21.53, p. 819). An endoscopic biopsy from the rectal wall is associated with a 2% risk of fistula formation. The extent of the lesion can be assessed by colonoscopy. Barium follow-through or MRI enterography can be of diagnostic value in showing small bowel strictures, ulcers and fistulae. Management Diarrhoea in the acute phase should be treated with codeine phosphate, diphenoxylate or loperamide. Antibiotics may be required for bacterial overgrowth. Nutritional supplements are necessary when malabsorption is present. Colestyramine or colesevelam is useful for bile acid diarrhoea. Surgery should be avoided, if possible, because the injured intestine is difficult to resect and anastomose, but may be necessary for obstruction, perforation or fistula. In radiation proctitis, the underlying pathophysiology is tissue ischaemia rather than inflammation; glucocorticoid enemas are therefore not effective. Traditionally, endoscopic argon plasma coagulation therapy was used but this is of limited benefit and can induce fistula, stricture or perforation. Effective treatments include sucralfate enema and hyperbaric oxygen. Abetalipoproteinaemia This rare autosomal recessive disorder is caused by deficiency of apolipoprotein B, which results in failure of chylomicron formation. Fig. 21.43 Consequences of ileal resection. Decreased bile salt pool, lithogenic bile leading to gallstones Impaired bile salt absorption leading to watery diarrhoea B12 malabsorption Increased absorption of oxalate Oxalate calculi Impaired micelle formation and fat malabsorption 21.47 Chronic complications of intestinal irradiation • Proctocolitis • Bleeding from telangiectasia • Small bowel strictures • Fistulae: rectovaginal, colovesical, enterocolic • Adhesions • Malabsorption: bacterial overgrowth, bile acid diarrhoea (ileal damage)

Intestinal lymphangiectasia This may be primary, resulting from congenital malunion of lymphatics, or secondary to lymphatic obstruction due to lymphoma, filariasis or constrictive pericarditis. Impaired drainage of intestinal lymphatic vessels leads to discharge of protein and fat-rich lymph into the gastrointestinal lumen. The condition presents with peripheral lymphoedema, pleural effusions or chylous ascites, and steatorrhoea. Investigations reveal hypoalbuminaemia, lymphopenia and reduced serum immunoglobulin concentrations. The diagnosis can be made by CT scanning and by enteroscopy with jejunal biopsy, which shows greatly dilated lacteals.

Treatment consists of a low-fat diet with medium-chain triglyceride supplements. Ulceration of the small intestine Small bowel ulcers are uncommon and are either idiopathic or secondary to underlying intestinal disorders (Box 21.50). Ulcers are more common in the ileum and cause bleeding, perforation, stricture formation or obstruction. Barium studies and enteroscopy confirm the diagnosis. rare diseases of enteric smooth muscle and nerves that can cause this syndrome. Management This is often difficult. Underlying causes should be addressed and further surgery avoided. Metoclopramide or domperidone may enhance motility and antibiotics are given for bacterial overgrowth. Nutritional and psychological support is also necessary. Miscellaneous disorders of the small intestine Protein-losing enteropathy This term is used when there is excessive loss of protein into the gut lumen, sufficient to cause hypoproteinaemia. Protein-losing enteropathy occurs in many gut disorders but is most common in those in which ulceration occurs (Box 21.49). In other disorders, protein loss can result from increased mucosal permeability or obstruction of intestinal lymphatic vessels. Patients present with peripheral oedema and hypoproteinaemia in the presence of normal liver function, low albumin and globulin, and without proteinuria. The diagnosis can be confirmed by measurement of faecal clearance of α1-antitrypsin or 51Cr-labelled albumin after intravenous injection. Other investigations should be performed to determine the underlying cause. Treatment is that of the underlying disorder, with nutritional support and measures to control peripheral oedema. 21.49 Causes of protein-losing enteropathy With mucosal erosions or ulceration • Crohn’s disease • Ulcerative colitis • Radiation damage • Oesophageal, gastric or colonic cancer • Lymphoma Without mucosal erosions or ulceration • Ménétrier’s disease • Bacterial overgrowth • Coeliac disease • Tropical sprue • Eosinophilic gastroenteritis • Systemic lupus erythematosus With lymphatic obstruction • Intestinal lymphangiectasia • Constrictive pericarditis • Lymphoma • Whipple’s disease 21.48 Causes of chronic intestinal pseudo-obstruction Primary or idiopathic • Rare familial visceral myopathies or neuropathies • Congenital aganglionosis Secondary • Drugs (opiates, tricyclic antidepressants, phenothiazines) • Smooth muscle disorders (systemic sclerosis, amyloidosis, mitochondrial myopathies) • Myenteric plexus disorders, e.g. paraneoplastic syndrome in small-cell lung cancer • Central nervous system disorders (Parkinson’s disease, autonomic neuropathy) • Endocrine and metabolic disorders (hypothyroidism, phaeochromocytoma, acute intermittent porphyria) 21.50 Causes of small intestinal ulcers • Idiopathic • Inflammatory bowel disease • Non-steroidal antiinflammatory drugs • Ulcerative jejuno-ileitis • Lymphoma and carcinoma • Infections (tuberculosis, typhoid, Yersinia enterocolitica) • Others (radiation, vasculitis) NSAID-associated small intestinal toxicity These drugs cause a spectrum of small intestinal lesions ranging from erosions and ulcers to mucosal webs, strictures and, rarely, a condition known as ‘diaphragm disease’, in which intense submucosal fibrosis results in circumferential stricturing. The condition can present with pain, obstruction, bleeding or anaemia, and may mimic Crohn’s disease, carcinoma or lymphoma. Enteroscopy or capsule endoscopy can reveal the diagnosis but sometimes this is discovered only at laparotomy. Eosinophilic gastroenteritis This disorder of unknown aetiology can affect any part of the gastrointestinal tract; it is characterised by eosinophil infiltration involving the gut wall, in the absence of parasitic infection or eosinophilia of other tissues. It may be mucosal, muscular or subserosal. Peripheral blood eosinophilia is present in 80% of cases. Clinical features There are features of obstruction and inflammation, such as colicky pain, nausea and vomiting, diarrhoea and weight loss. Protein-losing enteropathy occurs and up to 50% of patients have a history of other allergic disorders. Serosal involvement may produce eosinophilic ascites. Investigations and management The diagnosis is made by histological assessment of multiple endoscopic biopsies, although full-thickness biopsies are occasionally required. Other

investigations should be performed

812 • GASTROENTEROLOGY symptoms. Addition of commercial lactase preparations to milk has been effective in some studies but is costly. Intolerance of other sugars ‘Osmotic’ diarrhoea can be caused by sorbitol, an unabsorbable carbohydrate that is used as an artificial sweetener. Fructose contained within fruit juices may also cause diarrhoea if it is consumed in greater quantities than can be absorbed. Food allergy Food allergies are immune-mediated disorders, most commonly due to type I hypersensitivity reactions with production of IgE antibodies, although type IV delayed hypersensitivity reactions are also seen (p. 83). Up to 20% of the population perceive themselves as suffering from food allergy but only 1–2% of adults and 5–7% of children have genuine food allergies. The most common culprits are peanuts, milk, eggs, soya and shellfish. Clinical manifestations occur immediately on exposure and range from trivial to life-threatening or even fatal anaphylaxis. The common oral allergy syndrome results from contact with benzoic acid in certain fresh fruit juices, leading to urticaria and angioedema of the lips and oropharynx. This is not, however, an immune-mediated reaction. ‘Allergic gastroenteropathy’ has features similar to eosinophilic gastroenteritis, while ‘gastrointestinal anaphylaxis’ consists of nausea, vomiting, diarrhoea and sometimes cardiovascular and respiratory collapse. Fatal reactions to trace amounts of peanuts are well documented. The diagnosis of food allergy is difficult to prove or refute. Skin-prick tests and measurements of antigen-specific IgE antibodies in serum have limited predictive value. Double-blind placebo-controlled food challenges are the gold standard but are laborious and are not readily available. In many cases, clinical suspicion and trials of elimination diets are used. Treatment of proven food allergy consists of detailed patient education and awareness, strict elimination of the offending antigen, and, in some cases, antihistamines or sodium cromoglicate. Anaphylaxis should be treated as a medical emergency with resuscitation, airway support and intravenous adrenaline (epinephrine). Teachers and other carers of affected children should be trained to deal with this. Patients should wear an information bracelet and be taught to carry and use a preloaded adrenaline syringe. Infections of the small intestine Travellers’ diarrhoea, giardiasis and amoebiasis See pages 232, 287 and 286. Abdominal tuberculosis Mycobacterium tuberculosis is a rare cause of abdominal disease in Caucasians but must be considered in people in and from the developing world and in AIDS patients. Gut infection usually results from human M. tuberculosis, which is swallowed after coughing. Many patients have no pulmonary symptoms and a normal chest X-ray. The area most commonly affected is the ileocaecal region. The presentation and radiological findings may be very similar to those of Crohn’s disease. Abdominal pain can be acute or of several months’ duration but diarrhoea is less common in tuberculosis to exclude parasitic infection and other causes of eosinophilia. The serum IgE concentration is often raised. Dietary manipulations are rarely effective, although elimination diets, especially of milk, may benefit a few patients. Severe symptoms are treated with prednisolone (20–40 mg daily) and/or sodium cromoglicate, which stabilises mast cell membranes. The prognosis is good in the majority of patients. Meckel’s diverticulum This is the most common congenital anomaly of the gastrointestinal tract and occurs in 0.3–3% of people, but the vast majority of affected individuals are asymptomatic throughout life. The diverticulum results from failure of closure of the vitelline duct, with persistence of a blind-ending sac arising from the antimesenteric border of the ileum; it usually occurs within 100 cm of the ileocaecal valve and is up to 5 cm long. Approximately 50% contain ectopic gastric mucosa; rarely, colonic, pancreatic or endometrial tissue is present. Complications most commonly occur in the first 2 years of life but are occasionally seen in young adults. Bleeding can result from ulceration of ileal mucosa adjacent to the ectopic parietal cells and

presents as recurrent melaena or altered blood per rectum. The diagnosis can be made by scanning the abdomen using a gamma counter following an intravenous injection of 99mTc-pertechnetate, which is concentrated by ectopic parietal cells. Other complications include intestinal obstruction, diverticulitis, intussusception and perforation. Intervention is unnecessary unless complications occur. Adverse food reactions Adverse food reactions are common and are subdivided into food intolerance and food allergy, the former being much more common. In food intolerance, there is an adverse reaction to food that is not immune-mediated and results from pharmacological (histamine, tyramine or monosodium glutamate), metabolic (lactase deficiency) or other mechanisms (toxins or chemical contaminants in food). Lactose intolerance Human milk contains around 200 mmol/L (68 g/L) of lactose, which is normally digested to glucose and galactose by the brush border enzyme lactase prior to absorption. In most populations, enterocyte lactase activity declines throughout childhood. The enzyme is deficient in up to 90% of adult Africans, Asians and South Americans but only 5% of northern Europeans. In cases of genetically determined (primary) lactase deficiency, jejunal morphology is normal. ‘Secondary’ lactase deficiency occurs as a consequence of disorders that damage the jejunal mucosa, such as coeliac disease and viral gastroenteritis. Unhydrolysed lactose enters the colon, where bacterial fermentation produces volatile short-chain fatty acids, hydrogen and carbon dioxide. Clinical features In most people, lactase deficiency is completely asymptomatic. However, some complain of colicky pain, abdominal distension, increased flatus, borborygmi and diarrhoea after ingesting milk or milk products. Irritable bowel syndrome may be suspected but the correct diagnosis is suggested by clinical improvement on lactose withdrawal. The lactose hydrogen breath test is a useful non-invasive investigation. Dietary exclusion of lactose is recommended, although most sufferers are able to tolerate small amounts of milk without

most lesions of this type. Enteroscopy, capsule endoscopy, mesenteric angiography and CT also play a role in investigation. Treatment is by surgical resection. Neuro-endocrine tumours These are discussed in detail on page 678. Lymphoma Non-Hodgkin lymphoma (p. 964) may involve the gastrointestinal tract as part of more generalised disease or may rarely arise in the gut, the small intestine being most commonly affected. Lymphomas occur with increased frequency in patients with coeliac disease, HIV/AIDS and other immunodeficiency states. Most are of B-cell origin, although lymphoma associated with coeliac disease is derived from T cells (enteropathy-associated T-cell lymphoma). Colicky abdominal pain, obstruction and weight loss are the presenting features and perforation is also seen occasionally. Malabsorption is a feature of diffuse bowel involvement and hepatosplenomegaly is rare. The diagnosis is made by small bowel biopsy, radiological contrast studies and CT. Staging investigations should be performed as for lymphomas occurring elsewhere (p. 962). Surgical resection, where possible, is the treatment of choice, with radiotherapy and combination chemotherapy reserved for those with advanced disease. The prognosis depends largely on the stage at diagnosis, cell type, patient age and the presence of ‘B’ symptoms (fever, weight loss, night sweats). Immunoproliferative small intestinal disease Immunoproliferative small intestinal disease (IPSID), also known as alpha heavy chain disease, is a rare condition occurring mainly in Mediterranean countries, the Middle East, India, Pakistan and North America. It is a variant of B-cell lymphoma of MALT type and often associated with Campylobacter jejuni infection. The condition varies in severity from relatively benign to frankly malignant. The small intestinal mucosa is diffusely affected, especially proximally, by a dense

lymphoplasmacytic infiltrate. Enlarged mesenteric lymph nodes are also common. Most patients are young adults who present with malabsorption, anorexia and fever. Serum electrophoresis confirms the presence of alpha heavy chains (from the Fc portion of IgA). Prolonged remissions can be obtained with long-term antibiotic therapy but chemotherapy is required for those who fail to respond or who have aggressive disease. Inflammatory bowel disease Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases that pursue a protracted relapsing and remitting course, usually extending over years. The diseases have many similarities and it is sometimes impossible to differentiate between them. One crucial distinction is that ulcerative colitis involves only the colon, while Crohn's disease can involve any part of the gastrointestinal tract from mouth to anus. A summary of the main features of ulcerative colitis and Crohn's disease is provided in Box 21.51. The incidence of inflammatory bowel disease (IBD) varies widely between populations. There was a dramatic increase in the incidence of both ulcerative colitis and Crohn's disease in the Western world, starting in the second half of the last century and than in Crohn's disease. Low-grade fever is common but not invariable. Like Crohn's disease, tuberculosis can affect any part of the gastrointestinal tract and perianal disease with fistula is recognised. Peritoneal tuberculosis may result in peritonitis with exudative ascites, associated with abdominal pain and fever. Granulomatous hepatitis occurs. Investigations Abdominal tuberculosis causes an elevated ESR; a raised serum alkaline phosphatase concentration suggests hepatic involvement. Histological confirmation should be sought by endoscopy, laparoscopy or liver biopsy. Caseation of granulomas is not always seen and acid- and alcohol-fast bacteria are often scanty. Culture may be helpful but identification of the organism may take 6 weeks and diagnosis is now possible on biopsy specimens using PCR-based techniques. Management When the presentation is very suggestive of abdominal tuberculosis, chemotherapy with multiple anti-tuberculous drugs should be commenced, even if bacteriological or histological proof is lacking. Isoniazid, pyrazinamide and ethambutol is a common standard regime (p. 590), though the precise choice will be dependent on local drug resistance patterns. Cryptosporidiosis Cryptosporidiosis and other protozoal infections, including cystoisosporiasis (Cystoisospora belli) and microsporidiosis, are dealt with on pages 287 and 317. Tumours of the small intestine The small intestine is rarely affected by neoplasia and fewer than 5% of all gastrointestinal tumours occur at this site. Benign tumours The most common are adenomas, GISTs, lipomas and hamartomas. Adenomas are most often found in the periampullary region and are usually asymptomatic, although occult bleeding or obstruction due to intussusception may occur. Transformation to adenocarcinoma is rare. Multiple adenomas are common in the duodenum of patients with familial adenomatous polyposis (FAP), who merit regular endoscopic surveillance. Hamartomatous polyps with almost no malignant potential occur in Peutz–Jeghers syndrome (p. 829). Malignant tumours These are rare and include, in decreasing order of frequency, adenocarcinoma, neuro-endocrine tumours, malignant GIST and lymphoma. The majority occur in middle age or later. Kaposi's sarcoma of the small bowel may arise in patients with AIDS. Adenocarcinomas Adenocarcinomas occur with increased frequency in patients with FAP, coeliac disease, small bowel Crohn's disease and Peutz–Jeghers syndrome. This is a rare cancer, accounting for less than 5% of all gastrointestinal malignancies. The non-specific presentation and rarity of these lesions often lead to a delay in diagnosis. Despite advances in imaging and endoscopic techniques, early diagnosis is difficult. Barium follow-through examination or small bowel enterography studies demonstrate

 butyrate and other short-chain fatty acids. There is emerging evidence that the virome and mycobiome (fungal species) may be important in the development of IBD. In

both diseases, the intestinal wall is infiltrated with acute and chronic inflammatory cells, but there are important differences between the conditions in the distribution of lesions and in histological features (Fig. 21.45). coinciding with the introduction of a more ‘hygienic’ environment with the advent of domestic refrigeration and the widespread use of antibiotics. The developing world has seen similar patterns, as these countries adopt an increasingly Westernised lifestyle. In the West, the incidence of ulcerative colitis is stable at 10–20 per 100 000, with a prevalence of 100–200 per 100 000, while the incidence of Crohn’s disease is increasing and is now 5–10 per 100 000, with a prevalence of 50–100 per 100 000. Both diseases most commonly start in the second and third decades of life, with a second smaller incidence peak in the seventh decade. Approximately 240 000 people are affected by IBD in the UK (approximately 1.4 million in the USA), equating to a prevalence of about 1 in 250. Life expectancy in patients with IBD is similar to that of the general population. Although many patients require surgery and admission to hospital for other reasons, with substantial associated morbidity, the majority have an excellent work record and pursue a normal life. Pathophysiology IBD has both environmental and genetic components, and evidence from genome-wide association studies suggests that genetic variants that predispose to Crohn’s disease may have undergone positive selection by protecting against infectious diseases, including tuberculosis (Box 21.52). It is thought that IBD develops because these genetically susceptible individuals mount an abnormal inflammatory response to environmental triggers, such as intestinal bacteria. This leads to inflammation of the intestine with involvement of a wide array of innate and adaptive immune cell responses, with release of inflammatory mediators, including TNF-α, IL-12 and IL-23, which cause tissue damage (Fig. 21.44). There is an association between microbial dysbiosis and IBD. For example, there is a reduced diversity, primarily of Firmicutes and in particular, Faecalibacterium prausnitzii. Functional changes in the bacteria are important and include a reduction of anti-inflammatory metabolites, such as 21.51 Comparison of ulcerative colitis and Crohn’s disease Ulcerative colitis Crohn’s disease Age group Any Any Gender M = F Slight female preponderance Incidence Stable Increasing Ethnic group Any Any; more common in Ashkenazi Jews Genetic factors HLA-DR*103; colonic epithelial barrier function (HNF4α, LAMB1, CDH1) Defective innate immunity and autophagy (NOD2, ATG16L1, IRGM) Risk factors More common in non-/ex-smokers Appendicectomy protects More common in smokers Anatomical distribution Colon only; begins at anorectal margin with variable proximal extension Any part of gastrointestinal tract; perianal disease common; patchy distribution, skip lesions Extra-intestinal manifestations Common Common Presentation Bloody diarrhoea Variable; pain, diarrhoea, weight loss all common Histology Inflammation limited to mucosa; crypt distortion, cryptitis, crypt abscesses, loss of goblet cells Submucosal or transmural inflammation common; deep fissuring ulcers, fistulae; patchy changes; granulomas Management 5-ASA; glucocorticoids; azathioprine; biological therapy (anti-TNF, anti-α4β7 integrin); colectomy is curative Glucocorticoids; azathioprine; methotrexate; biological therapy (anti-TNF, anti-α4β7 integrin); nutritional therapy; smoking cessation; surgery for complications is not curative; 5-ASA is not effective (5-ASA = 5-aminosalicylic acid; TNF = tumour necrosis factor) 21.52 Factors associated with the development of inflammatory bowel disease Genetic • Both CD and UC are common in Ashkenazi Jews • 10% have first-degree relative/1 or more close relative with IBD • High concordance in identical twins (40–50% CD; 20–25% UC) • 163 susceptibility loci identified at genome-wide levels of significance; most confer susceptibility to both CD and UC; many are also susceptibility loci for other inflammatory conditions (especially ankylosing spondylosis and psoriasis) • UC and CD are both associated with genetic variants at HLA locus, and with multiple genes involved with immune signalling (especially IL-23 and IL-10 pathways) • CD is associated with genetic defects in innate

*immunity and autophagy (NOD2, ATG16L1 and IRGM genes) • UC is associated with genetic defects in barrier function • NOD2 is associated with ileal and stricturing disease, and hence a need for resectional surgery • HLA-DR*103 is associated with severe UC Environmental • UC is more common in non-smokers and ex-smokers • CD is more common in smokers (relative risk = 3) • CD is associated with a low-residue, high-refined-sugar diet • Commensal gut microbiota are altered (dysbiosis) in CD and UC • Appendicectomy protects against UC (CD = Crohn's disease; HLA = human leucocyte antigen; IBD = inflammatory bowel disease; IL = interleukin; UC = ulcerative colitis)

Ulcerative colitis Inflammation invariably involves the rectum (proctitis) and spreads proximally in a continuous manner to involve the entire colon in some cases (pancolitis). In long-standing pancolitis, the bowel can become shortened and post-inflammatory 'pseudopolyps' develop; these are normal or hypertrophied residual mucosa within areas of atrophy (Fig. 21.46). The inflammatory process is limited to the mucosa and spares the deeper layers of the bowel wall (Fig. 21.47). Both acute and chronic inflammatory cells infiltrate the lamina propria and the crypts ('cryptitis'). Crypt abscesses are typical. Goblet cells lose their mucus and, in long-standing Fig. 21.44 Pathogenesis of inflammatory bowel disease. (1) Bacterial antigens are taken up by specialised M cells, pass between leaky epithelial cells or enter the lamina propria through ulcerated mucosa. (2) After processing, they are presented to type 1 T-helper cells by antigenpresenting cells (APCs) in the lamina propria. (3) T-cell activation and differentiation results in a Th1 T cell-mediated cytokine response (4) with secretion of cytokines, including interferon gamma (IFN-γ). Further amplification of T cells perpetuates the inflammatory process with activation of non-immune cells and release of other important cytokines, including interleukin 12 (IL-12), IL-23, IL-1, IL-6 and tumour necrosis factor alpha (TNF-α). These pathways occur in all normal individuals exposed to an inflammatory insult and this is self-limiting in healthy subjects. In genetically predisposed persons, dysregulation of innate immunity may trigger inflammatory bowel disease. M cell APC Macrophage Type 1 Th cell IL-12 IL-23 IFN-γ IL-1 IL-6 TNF-α release

Fig. 21.45 Common patterns of disease distribution in inflammatory bowel disease. Left-sided colitis 30–40% Perianal disease alone < 10% Crohn's disease Ileal or ileocolonic 40% Small intestinal 30–40% Crohn's colitis c. 20% Ulcerative colitis Proctitis 40–50% Extensive colitis (up to pancolitis) 20% Fig. 21.46 Pseudopolyposis in ulcerative colitis.

 subacute or even acute intestinal obstruction. The pain is often associated with diarrhoea, which is usually watery and does not contain blood or mucus. Almost all patients lose weight because they avoid food, since eating provokes pain. Weight loss may also be due to malabsorption and some patients present with features of fat, protein or vitamin deficiencies. Crohn's colitis presents in an identical manner to ulcerative colitis but rectal cases, glands become distorted. Dysplasia, characterised by heaping of cells within crypts, nuclear atypia and increased mitotic rate, may herald the development of colon cancer. Crohn's disease The sites most commonly involved are, in order of frequency, the terminal ileum and right side of colon, colon alone, terminal ileum alone, ileum and jejunum. The entire wall of the bowel is oedematous and thickened, and there are deep ulcers that often appear as linear fissures; thus the mucosa between them is described as 'cobblestone'. These may penetrate through the bowel wall to

initiate abscesses or fistulae involving the bowel, bladder, uterus, vagina and skin of the perineum. The mesenteric lymph nodes are enlarged and the mesentery is thickened. Crohn's disease has a patchy distribution and the inflammatory process is interrupted by islands of normal mucosa. On histological examination, the bowel wall is thickened with a chronic inflammatory infiltrate throughout all layers (Fig. 21.48). Clinical features Ulcerative colitis The cardinal symptoms are rectal bleeding with passage of mucus and bloody diarrhoea. The presentation varies, depending on the site and severity of the disease (see Fig. 21.45), as well as the presence of extra-intestinal manifestations. The first attack is usually the most severe and is followed by relapses and remissions. Emotional stress, intercurrent infection, gastroenteritis, antibiotics or NSAID therapy may all provoke a relapse. Proctitis causes rectal bleeding and mucus discharge, accompanied by tenesmus. Some patients pass frequent, small-volume fluid stools, while others pass pellety stools due to constipation upstream of the inflamed rectum. Constitutional symptoms do not occur. Left-sided and extensive colitis causes bloody diarrhoea with mucus, often with abdominal cramps. In severe cases, anorexia, malaise, weight loss and abdominal pain occur and the patient is toxic, with fever, tachycardia and signs of peritoneal inflammation (Box 21.53). Crohn's disease The major symptoms are abdominal pain, diarrhoea and weight loss. Ileal Crohn's disease (Figs 21.49 and 21.50) may cause Fig. 21.47 Histology of ulcerative colitis. There is surface ulceration and inflammation is confined to the mucosa with excess inflammatory cells in the lamina propria, loss of goblet cells, and crypt abscesses (arrows). (SM = submucosa) SM Fig. 21.48 Histology of Crohn's disease. A Inflammation is 'transmural'; there is fissuring ulceration (arrow), with inflammation extending into the submucosa (SM). B At higher power, a characteristic non-caseating granuloma is seen. SM A B Fig. 21.49 Ileal Crohn's disease. Small bowel magnetic resonance image showing a terminal ileum that is thickened, narrowed and enhancing (arrow), with dilatation immediately proximal to this.

21.53 Assessment of disease severity in ulcerative colitis Mild Moderate Severe Daily bowel frequency < 4 4–6 ≥ 6* Blood in stools +/− +/++ +++ Stool volume < 200 g/24 hrs 200–400 g/24 hrs

> 400 g/24 hrs Pulse < 90 beats/min < 90 beats/min ≥ 90 beats/min* Temperature Normal Normal ≥ 37.8°C* Haemoglobin Normal Normal < 100 g/L (< 10 g/dL)* Erythrocyte sedimentation rate Normal Normal 30 mm/hr* (or equivalent C-reactive protein) Serum albumin 35 g/L (> 3.5 g/dL) < 30 g/L (< 3 g/dL) Abdominal X-ray Normal Normal Dilated bowel, mucosal islands, thumb-printing of mucosa, or absence of features Sigmoidoscopy Normal or erythema/granular mucosa Severe mucosal inflammatory changes; ulceration; blood in lumen *The Truelove–Witts criteria for acute severe ulcerative colitis are ≥ 6 bloody stools/24 hrs plus one or more of: anaemia, fever, tachycardia and high inflammatory markers. Fig. 21.50 Barium follow-through showing terminal ileal Crohn's disease. A long stricture is present (arrow A), and more proximally there is ulceration with characteristic 'rose thorn' ulcers (arrow B). A B Common; other causes are rare. 21.55 Differential diagnosis of small bowel Crohn's*

> *disease • Other causes of right iliac fossa mass: Caecal carcinoma Appendix abscess* • Infection (tuberculosis, Yersinia, actinomycosis) • Mesenteric adenitis • Pelvic inflammatory disease • Lymphoma 21.54 Conditions that can mimic ulcerative or Crohn's colitis Infective Bacterial • Salmonella • Shigella • Campylobacter jejuni • Escherichia coli O157 • Gonococcal proctitis • Pseudomembranous colitis • Chlamydia proctitis Viral • Herpes simplex proctitis • Cytomegalovirus Protozoal • Amoebiasis Non-infective • Ischaemic colitis • Collagenous colitis • Non-steroidal antiinflammatory drugs • Diverticulitis • Radiation proctitis • Behçet's disease • Colonic carcinoma sparing and the presence of perianal disease are features that favour a diagnosis of Crohn's disease. Many patients present with symptoms of both small bowel and colonic disease. A few patients present with isolated perianal disease, vomiting from jejunal strictures or severe oral ulceration. Physical examination often reveals evidence of weight loss, anaemia with glossitis and angular stomatitis. There is abdominal tenderness, most marked over the inflamed area. An abdominal mass may be palpable and is due to matted loops of thickened bowel or an intra-abdominal abscess. Perianal skin tags, fissures or fistulae are found in at least 50% of patients. Differential diagnosis The differential diagnosis is summarised in Box 21.54. The most important issue is to distinguish the first attack of acute colitis from infection. In general, diarrhoea lasting longer than 10 days in Western countries is unlikely to be the result of infection, whereas a history of foreign travel, antibiotic exposure (Clostridium difficile/pseudomembranous colitis) or homosexual contact increases the possibility of infection, which should be excluded by the appropriate investigations (see below). The diagnosis of Crohn's disease is usually more straightforward and is made on the basis of imaging and clinical presentation, but in atypical cases biopsy or surgical resection is necessary to exclude other diseases (Box 21.55).

 cumulative risk for dysplasia in ulcerative colitis may be as high as 20% after 30 years but is probably lower for Crohn's colitis. The risk is particularly high in patients who have concomitant primary sclerosing cholangitis for unknown reasons. Tumours develop in areas of dysplasia and may be multiple. Patients with long-standing colitis are therefore entered into surveillance programmes beginning 10 years after diagnosis. Targeted biopsies of areas that show abnormalities on staining with indigo carmine or methylene blue increase the chance of detecting dysplasia and this technique (termed pancolonic chromo-endoscopy) has replaced colonoscopy with random biopsies taken every 10 cm in screening for malignancy. The procedure allows patients to be stratified into high-, medium- or low-risk groups to determine the interval between surveillance procedures. Family history of colon cancer is also an important factor to consider. If high-grade dysplasia is found, panproctocolectomy is usually recommended because of the high risk of colon cancer. Extra-intestinal complications Extra-intestinal complications are common in IBD and may dominate the clinical picture. Some of these occur during relapse of intestinal disease; others appear to be unrelated to intestinal disease activity (Fig. 21.52). Investigations Investigations are necessary to confirm the diagnosis, define disease distribution and activity, and identify complications. Full blood count may show anaemia resulting from

bleeding or malabsorption of iron, folic acid or vitamin B12. Platelet count can also be high as a marker of chronic inflammation. Serum albumin concentration falls as a consequence of protein-losing enteropathy, inflammatory disease or poor nutrition. ESR and CRP are elevated in exacerbations and in response to abscess formation. Faecal calprotectin has a high sensitivity for detecting gastrointestinal inflammation and may be elevated, even when the CRP is normal. It is particularly useful for distinguishing inflammatory bowel disease from irritable bowel syndrome at diagnosis, and for subsequent monitoring of disease activity. Bacteriology At initial presentation, stool microscopy, culture and examination for Clostridium difficile toxin or for ova and cysts, blood cultures and serological tests should be performed. These investigations should be repeated in established disease to exclude superimposed enteric infection in patients who present with exacerbations of IBD. During acute flares necessitating hospital admission, three separate stool samples should be sent for bacteriology to maximise sensitivity. Endoscopy Patients who present with diarrhoea plus raised inflammatory markers or alarm features, such as weight loss, rectal bleeding and anaemia, should undergo ileocolonoscopy. Flexible sigmoidoscopy is occasionally performed to make a diagnosis, especially during acute severe presentations when ileocolonoscopy may confer an unacceptable risk; ileocolonoscopy should still be performed at a later date, however, in order to evaluate disease extent. In ulcerative colitis, there is loss of vascular pattern, granularity, friability and contact bleeding, with or without ulceration (Fig. 21.53). In Crohn’s disease, patchy inflammation, with discrete, deep ulcers, strictures and perianal disease (fissures, fistulae and skin tags), is typically observed, often with rectal sparing. In established disease, colonoscopy may show active inflammation Complications Life-threatening colonic inflammation This can occur in both ulcerative colitis and Crohn’s colitis. In the most extreme cases, the colon dilates (toxic megacolon) and bacterial toxins pass freely across the diseased mucosa into the portal and then systemic circulation. This complication arises most commonly during the first attack of colitis and is recognised by the features described in Box 21.53. An abdominal X-ray should be taken daily because, when the transverse colon is dilated to more than 6 cm (Fig. 21.51), there is a high risk of colonic perforation, although this complication can also occur in the absence of toxic megacolon. Severe colonic inflammation with toxic dilatation is a surgical emergency and most often requires colectomy. Haemorrhage Haemorrhage due to erosion of a major artery is rare but can occur in both conditions. Fistulae These are specific to Crohn’s disease. Enteroenteric fistulae can cause diarrhoea and malabsorption due to blind loop syndrome. Enterovesical fistulation causes recurrent urinary infections and pneumaturia. An enterovaginal fistula causes a faeculent vaginal discharge. Fistulation from the bowel may also cause perianal or ischiorectal abscesses, fissures and fistulae. Cancer The risk of dysplasia and cancer increases with the duration and extent of uncontrolled colonic inflammation. Thus patients who have long-standing, extensive colitis are at highest risk. Oral mesalazine therapy reduces the risk of dysplasia and neoplasia in ulcerative colitis. Azathioprine also seems to reduce the risk of colorectal cancer in ulcerative colitis and Crohn’s colitis. This protective effect probably extends to any medical treatment that results in sustained healing of the colonic mucosa. The Fig. 21.51 Plain abdominal X-ray showing a grossly dilated colon due to severe ulcerative colitis. There is also marked mucosal oedema and ‘thumb-printing’ (arrows).

Fig. 21.52 Systemic complications of inflammatory bowel disease. See also Chapters 17 and 18. (HLA = human leukocyte antigen) Unrelated to inflammatory bowel disease activity Autoimmune

hepatitis Primary sclerosing cholangitis and cholangiocarcinoma (ulcerative colitis) Gallstones Amyloidosis and oxalate calculi Sacroiliitis/ankylosing spondylitis (Crohn's with HLA-B27) Metabolic bone disease Occur during the active phase of inflammatory bowel disease Mouth ulcers Conjunctivitis Iritis Episcleritis Mesenteric or portal vein thrombosis Fatty liver Liver abscess/portal pyaemia Venous thrombosis Large-joint arthritis Erythema nodosum Pyoderma gangrenosum Fig. 21.53 Sigmoidoscopic view of moderately active ulcerative colitis. Mucosa is erythematous and friable with contact bleeding. Submucosal blood vessels are no longer visible. with pseudopolyps or a complicating carcinoma. Biopsies should be taken from each anatomical segment (terminal ileum, right colon, transverse colon, left colon and rectum) to confirm the diagnosis and define disease extent, and also to seek dysplasia in patients with long-standing colitis guided by pancolonic chromoendoscopy. In Crohn's disease, wireless capsule endoscopy is useful in the identification of small bowel inflammation but should be avoided in the presence of strictures. Enteroscopy may be required to make a histological diagnosis of small bowel Crohn's disease, when the inflamed segment is out of reach of standard endoscopes. All children and most adults with Crohn's disease should have upper gastrointestinal endoscopy and biopsy to complete their staging. Not only is upper gastrointestinal Crohn's disease relatively common in this group, but also it may help to make a definitive diagnosis in patients who otherwise appear to have non-specific colonic inflammation. Radiology Barium enema is a less sensitive investigation than colonoscopy in patients with colitis and, where colonoscopy is incomplete, a CT colonogram is preferred. Small bowel imaging is essential to complete staging of Crohn's disease. Traditional contrast imaging by barium follow-through demonstrates affected areas of the bowel as narrowed and ulcerated, often with multiple strictures (see Fig. 21.50). This has largely been replaced now by MRI enterography, which does not involve exposure to radiation and is a sensitive way of detecting extra-intestinal manifestations and of assessing pelvic and perineal involvement. These studies use an orally administered small bowel-distending agent and intravenous contrast to provide transmural imaging that can usefully distinguish between predominantly inflammatory strictures (that should respond to anti-inflammatory medical strategies)

 by laboratory testing: haemoglobin, white cell count, albumin, electrolytes, ESR and CRP, stool culture • radiologically: for colonic dilatation on plain abdominal X-rays. All patients should be given supportive treatment with intravenous fluids to correct dehydration and enteral nutritional support should be provided for malnourished patients (Box 21.57). Intravenous glucocorticoids (methylprednisolone 60 mg or hydrocortisone 400 mg/day) should be given by intravenous infusion or bolus injection. Topical and oral aminosalicylates have no role to play in the acute severe attack. Response to therapy is judged over the first 3 days. Patients who do not respond promptly to glucocorticoids should be considered for medical rescue therapy with ciclosporin (intravenous infusion or oral) or infliximab (5 mg/kg), which can avoid the need for urgent colectomy in approximately 60% of cases. Patients who develop colonic dilatation (> 6 cm), those whose clinical and laboratory measurements deteriorate and those who do not respond after 7–10 days' maximal medical treatment usually require urgent colectomy. Subtotal colectomy can also be performed laparoscopically, given sufficient local expertise. The surgical and medical teams should liaise early in the disease course and, if possible, the patient should have the opportunity to speak with the stoma nurse prior to colectomy. Maintenance of remission Life-long maintenance therapy is recommended for all patients with left-sided or extensive disease but is not necessary in those with proctitis (although 20% of these patients will develop proximal 'extension' over the lifetime of their disease). Once-daily oral 5-aminosalicylates are the preferred first-line

agents. Sulfasalazine has a higher incidence of side-effects but is equally effective and can be considered in patients with coexistent arthropathy. Patients who frequently relapse despite aminosalicylate drugs should be treated with thiopurines (azathioprine or 6-mercaptopurine). Biologic therapy with anti-TNF antibodies (infliximab or adalimumab) or anti-α4β7 integrin antibodies (vedolizumab) can also be considered for maintenance treatment in patients with moderate to severe ulcerative colitis who are intolerant of or non-responsive to thiopurine immunosuppression. Crohn's disease Principles of treatment Crohn's disease is a progressive condition that may result in stricture or fistula formation if suboptimally treated. It is therefore important to agree long-term treatment goals with the patient; these are to induce remission and then maintain glucocorticoid-free remission with a normal quality of life. Treatment should focus on monitoring the patient carefully for evidence of disease activity and complications (Box 21.58), and ensuring that mucosal healing is achieved. Induction of remission Glucocorticoids remain the mainstay of treatment for active Crohn's disease. The drug of first choice in patents with ileal disease is budesonide, since it undergoes 90% first-pass metabolism in the liver and has very little systemic toxicity. A typical regimen is 9 mg once daily for 6 weeks, with a gradual reduction in dose over the subsequent 2 weeks when therapy is stopped. If there is no response to budesonide within 2 weeks, the patient should be switched to prednisolone, which has greater potency. This is typically given in a dose of 40 mg daily, reducing by 5 mg/week over 8 weeks, at which point treatment is stopped. Oral prednisolone in the dose regimen described above is the treatment of choice for inducing remission and fibrotic strictures (that require a mechanical solution, such as surgical resection, stricturoplasty or endoscopic balloon dilatation). A plain abdominal X-ray is essential in the management of patients who present with severe active disease. Dilatation of the colon (see Fig. 21.51), mucosal oedema (thumb-printing) or evidence of perforation may be found. Patients with proctitis may have features of proximal faecal loading. In small bowel Crohn's disease, there may be evidence of intestinal obstruction or displacement of bowel loops by a mass. Ultrasound is a very powerful tool to detect small bowel inflammation and stricture formation but it is operator-dependent. The role of CT is limited to screening for complications, such as perforation or abscess formation, in the acutely unwell. Management Drugs that are used in the treatment of IBD are listed in Box 21.56. Although medical therapy plays an important role, optimal management depends on establishing a multidisciplinary teambased approach involving physicians, surgeons, radiologists, nurse specialists and dietitians. Both ulcerative colitis and Crohn's disease are life-long conditions and have important psychosocial implications; specialist nurses, counsellors and patient support groups have key roles in education, reassurance and coping. The key aims of medical therapy are to: • treat acute attacks (induce remission) • prevent relapses (maintain remission) • prevent bowel damage • detect dysplasia and prevent carcinoma • select appropriate patients for surgery. Ulcerative colitis Active proctitis Most patients with ulcerative proctitis respond to a 1 g mesalazine suppository but some will additionally require oral 5-aminosalicylate (5-ASA) therapy. Topical glucocorticoids are less effective and are reserved for patients who are intolerant of topical mesalazine. Patients with resistant disease may require treatment with systemic glucocorticoids and immunosuppressants. A stool softener may be required to treat proximal constipation. Active left-sided or extensive ulcerative colitis In mild to moderately active cases, the combination of a once-daily oral and a topical 5-ASA preparation ('top and tail approach') is usually effective. The topical preparation (1 g foam or liquid enema) is typically withdrawn after 1 month. The oral 5-ASA is continued long-term to prevent relapse and minimise the risk of dysplasia. In patients who do not respond to this approach within 2–4 weeks, oral prednisolone (40 mg daily, tapered by 5 mg/week over an 8-week total course) is indicated.

Glucocorticoids should never be used for maintenance therapy. At the first signs of glucocorticoid resistance (lack of efficacy) or in patients who require recurrent glucocorticoid doses to maintain control, immunosuppressive therapy with a thiopurine should be introduced. Simultaneous calcium and vitamin D supplementation should be given along with glucocorticoids for bone protection. Severe ulcerative colitis Patients who fail to respond to maximal oral therapy and those who present with acute severe colitis (meeting the Truelove–Witts criteria; see Box 21.53) are best managed in hospital and should be monitored jointly by a physician and surgeon: • clinically: for the presence of abdominal pain, temperature, pulse rate, stool blood and frequency

21.56 Drugs used in the treatment of inflammatory bowel disease Class Mechanism of action Notes Aminosalicylates (mesalazine (Asacol, Salofalk, Pentasa, Mezavant), olsalazine, sulfasalazine, balsalazide) Modulate cytokine release from mucosa Different means of delivery to colon: pH-dependent (Asacol, Salofalk) time-dependent (Pentasa) bacterial breakdown by colonic bacteria from a carrier molecule (sulfasalazine, balsalazide) No proven value in CD Available as oral or topical (enema/suppository) Sulfasalazine causes side-effects in 10–45%: headache, nausea, diarrhoea, blood dyscrasias Other aminosalicylates better tolerated; diarrhoea, headache in 2–5% Rarely, renal impairment (check urea and electrolytes 6-monthly) Glucocorticoids (prednisolone, hydrocortisone, budesonide) Anti-inflammatory Budesonide is a potent glucocorticoid efficiently cleared from circulation by liver, thereby minimising adrenocortical suppression and steroid side-effects Topical, oral or IV, according to disease severity Budesonide considered for active ileitis and ileocolitis High vigilance for complications Never used for maintenance therapy Calcium/vitamin D supplements Thiopurines (azathioprine, mercaptopurine) Immunomodulation by inducing T-cell apoptosis Azathioprine is metabolised in liver to mercaptopurine, then by TPMT to thioguanine nucleotides Effective 12 weeks after starting therapy Complications leading to drug withdrawal in approximately 20%: influenza-like syndrome with myalgia, nausea and vomiting; leucopenia in 3%, particularly in inherited TPMT deficiency; hepatotoxicity; pancreatitis 60% of those intolerant of azathioprine will tolerate mercaptopurine Increase in lymphoma (approximately 2–3-fold) and non-melanoma skin cancer (life-long sun protection advised) Check TPMT levels prior to starting treatment and avoid if deficient/ very low due to risk of toxicity Metabolite levels can be measured to tailor therapy Use with caution for patients presenting over the age of 60 years due to risk of malignancy Methotrexate Anti-inflammatory Intolerance in 10–18% Maximal efficacy when given by SC injection once weekly Nausea, stomatitis, diarrhoea, hepatotoxicity and pneumonitis Co-prescription of folic acid and antiemetics. Teratogenic; robust contraception required for males and females Ciclosporin Inhibits T-cell activation Rescue therapy to prevent surgery in UC responding poorly to glucocorticoids. No value in CD Major side-effects in 0–17%: nephrotoxicity, infections, neurotoxicity (including fits) Minor complications in up to 50%: tremor, paraesthesiae, abnormal liver function tests, hirsutism Anti-TNF antibodies (infliximab and adalimumab) Suppress inflammation and induce apoptosis of inflammatory cells Moderate to severe CD, including fistulating disease Moderate to severe UC and acute severe UC as rescue therapy Acute (anaphylactic) and delayed (serum sickness) infusion reactions after multiple infusions; anti-drug antibody titres and drug levels can be measured Contraindicated in infection; reactivation of latent tuberculosis and moderate to severe cardiac failure Increased risk of infections and possibly of malignancy Rarely, neurological adverse events Requires assessment for latent tuberculosis and hepatitis B and C prior to commencement Continue until treatment failure or 12 months and

reassess Anti-α4β7 integrin (vedolizumab) Blocks integrin expressed on leukocytes and inhibits interaction with gut-specific receptor on endothelium, reducing leukocyte migration to gut mucosa Moderate to severe CD or moderate to severe UC where treatment with anti-TNF has failed or is not tolerated Side-effects include nasopharyngitis, arthralgia, headache Progressive multifocal leukoencephalopathy risk is reduced due to gut specificity Induction with 300 mg infusion at weeks 0, 2 and 6; maintenance 8-weekly infusions thereafter Discontinue if no improvement after 14 weeks Continue until treatment failure or 12 months and reassess Antibiotics Antibacterial Useful in perianal CD and pouchitis Major concern is peripheral neuropathy with long-term metronidazole Antidiarrhoeal agents (loperamide, co-phenoxylate) Reduce gut motility and small bowel secretion Loperamide improves anal function Avoided in acute flare-ups of disease May precipitate colonic dilatation (CD = Crohn's disease; IV = intravenous; SC = subcutaneous; TNF = tumour necrosis factor; TPMT = thiopurine methyltransferase; UC = ulcerative colitis)

822 • GASTROENTEROLOGY of remission, a substantial proportion of patients (20–30%) remain well without the requirement for maintenance therapy. Patients with evidence of persistently active disease require further treatment (see below). Maintenance therapy Immunosuppressive treatment with thiopurines (azathioprine and mercaptopurine) forms the core of maintenance therapy but methotrexate is also effective and can be given once weekly, either orally or by subcutaneous injection. Women and men of child-bearing potential who are prescribed methotrexate must use a robust contraceptive method, and should be counselled to plan pregnancy with a 3-month methotrexate-free period prior to conception since it is teratogenic. Combination therapy with an immunosuppressant and an anti-TNF antibody is the most effective strategy but costs are high and there is an increased risk of serious adverse effects. In the UK, the use of anti-TNF therapy is limited to specific patient subgroups with severe disease (Box 21.59). Vedolizumab is a possible option in patients who have not responded to anti-TNF therapy. It is a humanised monoclonal antibody against anti-α4β7 integrin. The α4β7 is expressed on a specific subset of CD4+ leucocytes; vedolizumab binds to this integrin and blocks interaction with MAdCAM-1, expressed on gut endothelial cells, resulting in a reduced influx of immune cells to the inflamed gut mucosa. Serious systemic adverse effects, including progressive multifocal leukoencephalopathy, have been seen with other anti-integrin drugs (such as natalizumab) but this has not emerged with vedolizumab due to its gut specificity. Emerging novel medical therapies for Crohn's disease are currently in phase III clinical trials and are likely to be available for clinical use in the near future. These include ustekinumab (anti-p40, inhibiting both IL-12 and IL-23) and tofacitinib (a Janus kinase inhibitor that blocks pro-inflammatory cytokine signalling). Cigarette smokers with Crohn's disease should be strongly counselled to stop smoking at every possible opportunity. Those that do not manage to stop smoking fare much worse, with increased rates of relapse and surgical intervention. Careful monitoring of disease activity (see Box 21.58) is the key to maintaining sustained remission and preventing the accumulation of bowel damage in Crohn's disease. in colonic Crohn's disease. Calcium and vitamin D supplements should be co-prescribed in patients who are on glucocorticoids, to try to compensate for their inhibitory effect on intestinal calcium absorption. As an alternative to glucocorticoid therapy, enteral nutrition with either an elemental (constituent amino acids) or polymeric (liquid protein) diet may induce remission. Both types of diet are equally effective but the polymeric one is more palatable when taken by mouth. It is particularly effective in children, in whom equal efficacy to glucocorticoids has been demonstrated, and in extensive ileal disease in adults. As well as resting the gut and providing excellent nutritional support, it also has a direct anti-inflammatory effect. It is an effective bridge to urgent

staging investigations at first presentation and can be given by mouth or by nasogastric tube. With sufficient explanation, encouragement and motivation, most patients will tolerate it well. Some individuals with severe colonic disease require admission to hospital for intravenous glucocorticoids. In severe ileal or panenteric disease, induction therapy with an anti-TNF agent is appropriate, provided that acute perforating complications, such as abscess, have not arisen. Both infliximab and adalimumab are licensed for use in the UK. Randomised trials have demonstrated that combination therapy with an anti-TNF antibody and a thiopurine is the most effective strategy for inducing and maintaining remission in luminal Crohn's patients. This strategy is more effective than anti-TNF monotherapy, which, in turn, is more effective than thiopurine monotherapy. Following induction 21.58 Monitoring of inflammatory bowel disease (IBD) • Assess symptoms, including extra-intestinal manifestations • Examine for abdominal mass or perianal disease • Perform full blood count, urea and electrolytes, liver function tests, albumin, C-reactive protein (CRP) • Check haematinics (vitamin B12, folate, iron studies) at least annually • Check faecal calprotectin (to monitor each disease flare/change in therapy and assess response) • Perform stool cultures (at each flare to exclude infection) • Assess mucosal healing: surrogate markers (CRP/calprotectin), ileocolonoscopy and/or small bowel magnetic resonance imaging • Enrol patient in a dedicated IBD clinic (monitoring of stable, uncomplicated patients may be carried out by a nurse or phone clinic) • Arrange IBD multidisciplinary meeting for acutely ill or complex patients • Check vaccinations are up to date; ensure surveillance colonoscopy is scheduled where appropriate 21.57 Medical management of fulminant ulcerative colitis • Admit to hospital for intensive therapy and monitoring • Give IV fluids and correct electrolyte imbalance • Consider transfusion if haemoglobin is < 100 g/L (< 10 g/dL) • Give IV methylprednisolone (60 mg daily) or hydrocortisone (400 mg daily) • Give antibiotics until enteric infection is excluded • Arrange nutritional support • Give subcutaneous low-molecular-weight heparin for prophylaxis of venous thromboembolism • Avoid opiates and antidiarrhoeal agents • Consider infliximab (5 mg/kg) or ciclosporin (2 mg/kg) in stable patients not responding to 3–5 days of glucocorticoids 21.59 How to give anti-tumour necrosis factor (TNF) therapy in inflammatory bowel disease • Infliximab (5 mg/kg IV infusion) is given as three loading doses (at 0, 2 and 6 weeks), with 8-weekly maintenance thereafter • Adalimumab is given as SC injections, which patients can be trained to give themselves. Loading dose is 160 mg, followed by 80 mg 2 weeks later and 40 mg every second week thereafter; some patients require dose escalation to 40 mg once weekly • Concomitant immunosuppression with a thiopurine or methotrexate may be more efficacious than monotherapy but has more side-effects • Anti-TNF therapy is contraindicated in the presence of active infection and latent tuberculosis without appropriate prophylaxis; it carries an increased risk of opportunistic infections and a possible increased risk of malignancy; rarely, multiple sclerosis may be unmasked in susceptible individuals. Counselling about the balance of risk and benefit for each patient is important • Prior to therapy, latent tuberculosis must be excluded • Live vaccines should not be given • Certolizumab is effective for luminal Crohn's disease but is not licensed in Europe • Etanercept is not effective in Crohn's disease

Surgery should be as conservative as possible in order to minimise the loss of viable intestine and to avoid the creation of a short bowel syndrome (p. 708). Obstructing or fistulating small bowel disease may require resection of affected tissue. Patients who have localised segments of Crohn's colitis may be managed by segmental resection and/or multiple stricturoplasties, in which the

stricture is not resected but instead incised in its longitudinal axis and sutured transversely. Others who have extensive colitis require total colectomy but ileal–anal pouch formation should be avoided because of the high risk of recurrence within the pouch and subsequent fistulae, abscess formation and pouch failure. Historical datasets show that around 80% of Crohn's patients undergo surgery at some stage and 70% of these require more than one operation during their lifetime. Clinical recurrence following resectional surgery is present in 50% of all cases at 10 years. Emerging data demonstrate that aggressive medical therapy, coupled with intense monitoring, probably reduces the requirement for surgery substantially. IBD in special circumstances Childhood Chronic ill health in childhood or adolescent IBD may result in growth failure, metabolic bone disease and delayed puberty. Loss of schooling and social contact, as well as frequent hospitalisation, can have important psychosocial consequences. Treatment is similar to that described for adults and may require glucocorticoids, immunosuppressive drugs, biological agents and surgery. Monitoring of height, weight and sexual development is crucial. Children with IBD should be managed by specialised paediatric gastroenterologists and transitioned to adult care in dedicated clinics (Box 21.61). Pregnancy A women's ability to become pregnant is adversely affected by active IBD. Pre-conceptual counselling should focus on optimising disease control. During pregnancy, the rule of thirds applies: roughly one-third of women improve, one-third get worse and one-third remain stable with active disease. In the post-partum period, these changes sometimes reverse spontaneously. Drug therapy, including aminosalicylates, glucocorticoids and Fistulae and perianal disease Fistulae may develop in relation to active Crohn's disease and are often associated with sepsis. The first step is to define the site by imaging (usually MRI of the pelvis). Surgical exploration by an examination under anaesthetic is usually then required, to delineate the anatomy and drain abscesses. Seton sutures can be inserted through fistula tracts to ensure adequate drainage and to prevent future sepsis. Glucocorticoids are ineffective. Use of antibiotics, such as metronidazole and/ or ciprofloxacin, can aid healing as an adjunctive treatment. Thiopurines can be used in chronic disease but do not usually result in fistula healing. Infliximab and adalimumab can heal fistulae and perianal disease in many patients and are indicated when the measures described above have been ineffective. Other options for refractory perianal disease are proctectomy or diverting colostomy. Surgical treatment Ulcerative colitis Up to 60% of patients with extensive ulcerative colitis eventually require surgery. The indications are listed in Box 21.60. Impaired quality of life, with its impact on occupation and social and family life, is the most important of these. Surgery involves removal of the entire colon and rectum, and cures the patient. One-third of those with pancolitis undergo colectomy within 5 years of diagnosis. Before surgery, patients must be counselled by doctors, stoma nurses and patients who have undergone similar surgery. The choice of procedure is either panproctocolectomy with ileostomy, or proctocolectomy with ileal–anal pouch anastomosis. The sister text to this book, Principles and Practice of Surgery, should be consulted for further details. Crohn's disease The indications for surgery are similar to those for ulcerative colitis. Operations are often necessary to deal with fistulae, abscesses and perianal disease, and may also be required to relieve small or large bowel obstruction. In contrast to ulcerative colitis, surgery is not curative and disease recurrence is the rule. The only method that has consistently been shown to reduce post-operative recurrence is smoking cessation. Antibiotics are effective in the short term only. Use of thiopurines post-surgery is suggested if there are indicators of a high chance of recurrence, i.e. more than one resection or evidence of penetrating disease, such as fistulae or abscess. Otherwise, it is common to undertake colonoscopy 6 months after surgery to inspect and biopsy the anastomosis and neo-terminal ileum. Patients with endoscopic recurrence are then prescribed thiopurines. 21.60 Indications for surgery

in ulcerative colitis Impaired quality of life • Loss of occupation or education • Disruption of family life Failure of medical therapy • Dependence on oral glucocorticoids • Complications of drug therapy Fulminant colitis Disease complications unresponsive to medical therapy • Arthritis • Pyoderma gangrenosum Colon cancer or severe dysplasia 21.61 Inflammatory bowel disease in adolescence • Delayed growth and pubertal development: chronic active inflammation, malabsorption, malnutrition and long-term glucocorticoids contribute to short stature and delayed development, with physical and psychological consequences. • Metabolic bone disease: more common with chronic disease beginning in childhood, resulting from chronic inflammation, dietary deficiency and malabsorption of calcium and vitamin D. • Drug side-effects and adherence issues: young people are more likely to require azathioprine or biological therapy than adults. Poor adherence to therapy is more common than with adults, as younger patients may feel well, lack self-motivation to adhere and believe that drugs are ineffective or cause side-effects. • Loss of time from education: physical illness, surgery, fatigue in chronic inflammatory bowel disease, privacy and dignity issues, and social isolation may all contribute. • Emotional difficulties: may result from challenges in coping with illness, problems with forming interpersonal relationships, and issues relating to body image or sexual function.

 appearances are normal but histological examination of biopsies shows a range of abnormalities. It is therefore recommended that biopsies of the right and left colon plus the terminal ileum should be undertaken in all patients undergoing colonoscopy for diarrhoea. Collagenous colitis is characterised by the presence of a submucosal band of collagen, often with a chronic inflammatory infiltrate. The disease is more common in women and may be associated with rheumatoid arthritis, diabetes, coeliac disease and some drug therapies, such as NSAIDs or PPIs. Treatment with budesonide or 5-aminosalicylates is usually effective but the condition will recur in some patients on discontinuation of therapy. Irritable bowel syndrome Irritable bowel syndrome (IBS) is characterised by recurrent abdominal pain in association with abnormal defecation in the absence of a structural abnormality of the gut. About 10–15% of the population are affected at some time but only 10% of these consult their doctors because of symptoms. Nevertheless, IBS is the most common cause of gastrointestinal referral and accounts for frequent absenteeism from work and impaired quality of life. Young women are affected 2–3 times more often than men. Coexisting conditions, such as non-ulcer dyspepsia, chronic fatigue syndrome, dysmenorrhoea and fibromyalgia, are common. IBS is sometimes associated with a history of physical or sexual abuse and this is an important aspect of the history as these patients benefit from psychologically based therapy. Pathophysiology The cause of IBS is incompletely understood but biopsychosocial factors are thought to play an important role, along with luminal factors, such as diet and the gut microbiota, as discussed below. Behavioural and psychosocial factors Most patients seen in general practice do not have psychological problems but about 50% of patients referred to hospital have a psychiatric illness, such as anxiety, depression, somatisation and neurosis. Panic attacks are also common. Acute psychological stress and overt psychiatric disease are known to alter visceral perception and gastrointestinal motility. There is an increased prevalence of abnormal illness behaviour, with frequent consultations for minor symptoms and reduced coping ability (p. 1202). These factors contribute to but do not cause IBS. Physiological factors There is some evidence that IBS may be a serotoninergic (5-HT) disorder, as evidenced by relatively excessive release of 5-HT in diarrhoea-predominant IBS (D-IBS) and relative deficiency with constipation-predominant IBS (C-IBS). Accordingly, 5-HT3 receptor antagonists are effective in D-IBS, while 5-HT4 agonists improve bowel function in C-IBS. There is some evidence that IBS may

represent a state of low-grade gut inflammation or immune activation, not detectable by tests, with raised numbers of mucosal mast cells that sensitise enteric neurons by releasing histamine and tryptase. Some patients respond positively to mast cell stabilisers, such as ketotifen, which supports a pathogenic role of mast cells in at least some patients. Immune activation may be associated with altered CNS processing of visceral pain signals. This is more common in women and in D-IBS, and may be triggered by a prior episode of gastroenteritis with Salmonella or Campylobacter species. azathioprine, can be safely continued throughout pregnancy but methotrexate must be avoided, both during pregnancy and if the patient is trying to conceive (Box 21.62). Anti-TNF agents are transmitted through the placenta (but not breast milk) and are omitted during the last trimester. Metabolic bone disease Patients with IBD are prone to developing osteoporosis due to the effects of chronic inflammation, glucocorticoids, weight loss, malnutrition and malabsorption. Osteomalacia can also occur in Crohn's disease that is complicated by malabsorption, but is less common than osteoporosis. The risk of osteoporosis increases with age and with the dose and duration of glucocorticoid therapy. Refractory Crohn's disease Crohn's disease can be progressive despite maximal medical therapy and extensive surgery. There are several other immunomodulatory drugs in the clinical trial pipeline (see above). Microscopic colitis Microscopic colitis, which comprises two related conditions called lymphocytic colitis and collagenous colitis, has no known cause. The presentation is with watery diarrhoea. The colonoscopic 21.62 Pregnancy and inflammatory bowel disease (IBD) Pre-conception • Outcomes are best when pregnancy is carefully planned and disease is in remission • Methotrexate must be stopped 3 months prior to conception; other IBD drugs should be continued until discussed with a specialist • Aminosalicylates and azathioprine are safe in pregnancy • Glucocorticoids are probably safe • Anti-tumour necrosis factor biological therapy in pregnancy can continue if established pre-pregnancy but should be withheld in the third trimester due to placental transfer of antibody • No data are available for the use of vedolizumab in pregnancy • Daily high-dose (> 2 mg) folic acid supplements are recommended Pregnancy • Two-thirds of patients in remission will remain so in pregnancy • Active disease is likely to remain active • Severe active disease carries an increased risk of premature delivery and low birth weight • Gentle flexible sigmoidoscopy is safe after the first trimester • X-rays can be performed if clinically indicated but discuss with the radiologist first • Colonoscopy can be performed safely if the potential benefits outweigh the risks Labour • This needs careful discussion between patient, gastroenterologist and obstetrician • Normal labour and vaginal delivery are possible for most • Caesarean section may be preferred for patients with perianal Crohn's or an ileo-anal pouch to reduce risks of pelvic floor damage, fistulation and late incontinence Breastfeeding • This is safe and does not exacerbate IBD • Data on the risk to babies from drugs excreted in breast milk are limited; most of these drugs are probably safe • Patients should discuss breastfeeding and drug therapy with their doctor

or without sigmoidoscopy, are usually done and are normal in IBS. Colonoscopy should be undertaken in older patients (over 40 years of age) to exclude colorectal cancer. Endoscopic examination is also required in patients who report rectal bleeding to exclude colon cancer and IBD. Those who present atypically require investigations to exclude other gastrointestinal diseases. Diarrhoea-predominant patients justify investigations to exclude coeliac disease (p. 805), microscopic colitis (p. 824), lactose intolerance (p. 812), bile acid diarrhoea (p. 809), thyrotoxicosis (p. 635) and, in developing countries, parasitic infection. Management The most important steps

are to make a positive diagnosis and reassure the patient. Many people are concerned that they have developed cancer. A cycle of anxiety leading to colonic symptoms, which further heighten anxiety, can be broken by explaining that symptoms are not due to a serious underlying disease but instead are the result of behavioural, psychosocial, physiological and luminal factors. In individuals who fail to respond to reassurance, treatment is traditionally tailored to the predominant symptoms (Fig. 21.54). Dietary management is effective for many patients (Box 21.65). Up to 20% may benefit from a wheat-free diet, some may respond to lactose exclusion, and excess intake of caffeine or artificial sweeteners, such as sorbitol, should be addressed. A more restrictive, 'low-FODMAP' diet, supervised by a dietitian, with gradual re-introduction of different food groups, may help some patients, as may a trial of a gluten-free diet. Probiotics, in capsule form, can be effective if taken for several months, although the optimum combination of bacterial strains and dose have yet to be clarified. Patients with intractable symptoms sometimes benefit from several months of therapy with a tricyclic antidepressant, such as amitriptyline or imipramine (10–25 mg orally at night). Side-effects include dry mouth and drowsiness but these are usually mild and the drug is generally well tolerated, although patients with features of somatisation tolerate the drug poorly and lower doses should be used. It may act by reducing visceral sensation and by altering gastrointestinal motility. Anxiety and affective disorders may also require specific treatment (pp. 1200 and 1198). The 5-HT4 agonist prucalopride, the guanylate cyclase-C receptor agonist linaclotide, and chloride channel activators, such as lubiprostone, can be effective in constipation- predominant IBS. Trials of anti-inflammatory agents, such as ketotifen or mesalazine, and the antibiotic rifaximin may be considered in 21.63 Rome III criteria for diagnosis of irritable bowel syndrome Recurrent abdominal pain or discomfort on at least 3 days per month in the last 3 months, associated with two or more of the following: • Improvement with defecation • Onset associated with a change in frequency of stool • Onset associated with a change in form (appearance) of stool Luminal factors Both quantitative and qualitative alterations in intestinal bacterial microbiota have been reported. Small intestinal bacterial overgrowth (SIBO) may be present in some patients and lead to symptoms. This 'gut dysbiosis' may explain the response to probiotics or the non-absorbable antibiotic rifaximin. Dietary factors are also important. Some patients have chemical food intolerances (not allergy) to poorly absorbed, short-chain carbohydrates (lactose, fructose and sorbitol, among others), collectively known as FODMAPs (fermentable oligo-, di- and monosaccharides, and polyols). Their fermentation in the colon leads to bloating, pain, wind and altered bowel habit. Non-coeliac gluten sensitivity (negative coeliac serology and normal duodenal biopsies) seems to be present in some IBS patients, while others may be intolerant of chemicals such as salicylates or benzoates, found in certain foods. Clinical features The most common presentation is that of recurrent abdominal discomfort (Box 21.63). This is usually colicky or cramping in nature, felt in the lower abdomen and relieved by defecation. Abdominal bloating worsens throughout the day; the cause is unknown but it is not due to excessive intestinal gas. The bowel habit is variable. Most patients alternate between episodes of diarrhoea and constipation but it is useful to classify them as having predominantly constipation or predominantly diarrhoea. Those with constipation tend to pass infrequent pellety stools, usually in association with abdominal pain or proctalgia. Those with diarrhoea have frequent defecation but produce low-volume stools and rarely have nocturnal symptoms. Passage of mucus is common but rectal bleeding does not occur. Patients do not lose weight and are constitutionally well. Physical examination is generally unremarkable, with the exception of variable tenderness to palpation. Investigations The diagnosis is clinical in nature and can be made confidently in most patients using the Rome criteria combined with the absence of alarm symptoms, without resorting to

complicated tests (Box 21.64). Full blood count and faecal calprotectin, with 21.64 Supporting diagnostic features and alarm features in irritable bowel syndrome Features supporting a diagnosis of IBS • Presence of symptoms for more than 6 months • Frequent consultations for non-gastrointestinal problems • Previous medically unexplained symptoms • Worsening of symptoms by stress Alarm features • Age > 50 years; male gender • Weight loss • Nocturnal symptoms • Family history of colon cancer • Anaemia • Rectal bleeding 21.65 Dietary management of irritable bowel syndrome • Eat regularly and avoid missing meals • Take time to eat • Ensure adequate hydration and avoid carbonated and caffeinated drinks • Reduce alcohol intake • Reduce intake of 'resistant' starch and insoluble fibre • Avoid foods with artificial sweeteners • Consider a wheat-free diet • Consider a lactose exclusion diet • Consider a diet low in FODMAPs (FODMAPs = fermentable oligo-, di- and monosaccharides, and polyols)

826 • GASTROENTEROLOGY some patients with difficult symptoms but are best prescribed only after specialist referral. Psychological interventions, such as cognitive behavioural therapy, relaxation and gut-directed hypnotherapy, should be reserved for the most difficult cases. A range of complementary and alternative therapies exist; most lack a good evidence base but are popular and help some patients (Box 21.66). Most patients have a relapsing and remitting course. Exacerbations often follow stressful life events, occupational dissatisfaction and difficulties with interpersonal relationships. HIV/AIDS and the gastrointestinal tract Patients with HIV/AIDS may develop several symptoms referable to the gastrointestinal tract, as discussed in detail on page 316. HIV testing should be considered in all patients with atypical or unexplained gastrointestinal symptoms and in those resident in areas of high prevalence. Fig. 21.54 Management of irritable bowel syndrome. (FODMAP = fermentable oligo-, di- and monosaccharides, and polyols) • Duloxetine 30–60 mg at night • Relaxation therapy • Biofeedback • Hypnotherapy Symptoms persist Spasmolytic drugs • Mebeverine • Peppermint oil • Hyoscine • Probiotics • Rifaximin 600 mg daily for 2 weeks • Amitriptyline or imipramine 10–25 mg at night • Amitriptyline or imipramine 10–25 mg at night • Rifaximin 600 mg daily for 2 weeks Dietary changes • Low-FODMAP diet • Exclude wheat • Exclude dairy • Gluten-free diet Irritable bowel syndrome confirmed Reassurance Symptoms resolve Symptoms persist Constipation predominant Diarrhoea predominant Pain and bloating Avoid legumes and excessive dietary fibre. Consider trials of low-FODMAP or gluten-free diet Antidiarrhoeal drugs • Loperamide 2–8 mg daily • Codeine phosphate 30–90 mg daily • Colestyramine 1 sachet daily Symptoms persist Symptoms persist Symptoms persist Symptoms persist High-roughage diet Symptoms persist Ispaghula or psyllium Lactulose and/or macrogol Prucalopride or linaclotide 21.66 Complementary and alternative therapies for irritable bowel syndrome Manipulative and body-based • Massage, chiropractic Mind–body interventions • Meditation, hypnosis*, cognitive therapy Biologically based • Herbal products*, dietary additives, probiotics* Energy healing • Biofield therapies (reiki), bio-electromagnetic field therapies Alternative medical systems • Ayurveda, homeopathy, traditional Chinese medicine *Some evidence for benefit exists. From Hussain Z, Quigley EMM. Systematic review: complementary and alternative medicine in the irritable bowel syndrome. Aliment Pharmacol Ther 2006; 23:465–471.

is established by colonoscopy within 48 hours of presentation; otherwise, mucosal ulceration may have resolved. Resection is required for peritonitis. Chronic mesenteric ischaemia This results from atherosclerotic stenosis of the coeliac axis, superior mesenteric artery and inferior mesenteric

artery. At least two of the three vessels must be affected for symptoms to develop. The typical presentation is with dull but severe mid- or upper abdominal pain developing about 30 minutes after eating. Weight loss is common because patients are reluctant to eat and some experience diarrhoea. Physical examination shows evidence of generalised arterial disease. An abdominal bruit is sometimes audible but is non-specific. The diagnosis is made by mesenteric angiography. Treatment is by vascular reconstruction or percutaneous angioplasty, if the patient's clinical condition permits. The condition is frequently complicated by intestinal infarction, if left untreated. Disorders of the colon and rectum Tumours of the colon and rectum Polyps and polyposis syndromes Polyps may be neoplastic or non-neoplastic. The latter include hamartomas, metaplastic ('hyperplastic') polyps and inflammatory polyps. These have no malignant potential. Polyps may be single or multiple and vary from a few millimetres to several centimetres in size. Colorectal adenomas are extremely common in the Western world and the prevalence rises with age; 50% of people over 60 years of age have adenomas, and in half of these the polyps are multiple. They are more common in the rectum and distal colon and are either pedunculated or sessile. Histologically, they are classified as either tubular, villous or tubulovillous, according to the glandular architecture. Nearly all forms of colorectal carcinoma develop from adenomatous polyps, although not all polyps carry the same degree of risk. Features associated with a higher risk of subsequent malignancy are listed in Box 21.67. Adenomas are usually asymptomatic and discovered incidentally. Occasionally, they cause bleeding and anaemia. Villous adenomas can secrete large amounts of mucus, causing diarrhoea and hypokalaemia. Discovery of a polyp at sigmoidoscopy is an indication for colonoscopy because proximal polyps are present in 40–50% of such patients. Colonoscopic polypectomy should be carried out wherever possible, as this considerably reduces subsequent colorectal cancer risk (Fig. 21.55). Very large or sessile polyps can sometimes be removed safely by endoscopic mucosal resection (EMR) but many require surgery. Once all polyps have been removed, surveillance colonoscopy should be undertaken at 3–5-year intervals, as new polyps develop in 50% of patients. Patients over 75 years of age do not require repeated colonoscopies, as their subsequent lifetime cancer risk is low. Ischaemic gut injury Ischaemic gut injury is usually the result of arterial occlusion. Severe hypotension and venous insufficiency are less frequent causes. The presentation is variable, depending on the different vessels involved and the acuteness of the event. Diagnosis is often difficult. Acute small bowel ischaemia An embolus from the heart or aorta to the superior mesenteric artery is responsible for 40–50% of cases, thrombosis of underlying atheromatous disease for approximately 25%, and non-occlusive ischaemia due to hypotension complicating myocardial infarction, heart failure, arrhythmias or sudden blood loss for approximately 25%. Vasculitis and venous occlusion are rare causes. The clinical spectrum ranges from transient alteration of bowel function to transmural haemorrhagic necrosis and gangrene. Patients usually have evidence of cardiac disease and arrhythmia. Almost all develop abdominal pain that is more impressive than the physical findings. In the early stages, the only physical signs may be a silent, distended abdomen or diminished bowel sounds, with peritonitis developing only later. Leucocytosis, metabolic acidosis, hyperphosphataemia and hyperamylasaemia are typical. Plain abdominal X-rays show 'thumb-printing' due to mucosal oedema. Mesenteric or CT angiography reveals an occluded or narrowed major artery with spasm of arterial arcades, although most patients undergo laparotomy on the basis of a clinical diagnosis without angiography. Resuscitation, management of cardiac disease and intravenous antibiotic therapy, followed by laparotomy, are key steps. If treatment is instituted early, embolectomy and vascular reconstruction may salvage some small bowel. In these rare cases, a 'second look' laparotomy should be undertaken 24 hours later and further necrotic bowel

resected. In patients at high surgical risk, thrombolysis may sometimes be effective. The results of therapy depend on early intervention; patients treated late have a 75% mortality rate. Survivors often have nutritional failure from short bowel syndrome (p. 708) and require intensive nutritional support, including home parenteral nutrition and anticoagulation. Small bowel transplantation can be considered in selected patients. Patients with mesenteric venous thrombosis also require surgery if there are signs of peritonitis but are otherwise treated with anticoagulation. Investigations for underlying prothrombotic disorders should be performed (p. 978). Acute colonic ischaemia The splenic flexure and descending colon have little collateral circulation and lie in 'watershed' areas of arterial supply. The spectrum of injury ranges from reversible colopathy to transient colitis, colonic stricture, gangrene and fulminant pancolitis. Arterial thromboembolism is usually responsible but colonic ischaemia can also follow severe hypotension, colonic volvulus, strangulated hernia, systemic vasculitis or hypercoagulable states. Ischaemia of the descending and sigmoid colon is also a complication of abdominal aortic aneurysm surgery (where the inferior mesenteric artery is ligated). The patient is usually elderly and presents with sudden onset of cramping, left-sided, lower abdominal pain and rectal bleeding. Symptoms usually resolve spontaneously over 24–48 hours and healing occurs in 2 weeks. Some may develop a fibrous stricture or segment of colitis. A minority develop gangrene and peritonitis. The diagnosis 21.67 Risk factors for malignant change in colonic polyps • Large size (> 2 cm) • Multiple polyps • Villous architecture • High-grade dysplasia

 accounting for 1% of all colorectal cancers. It results from germline mutation of the tumour suppressor APC gene, followed by acquired mutation of the remaining allele (Ch. 3). The APC gene is large and over 1400 different mutations have been reported, but most are loss-of-function mutations resulting in a truncated APC protein. This protein normally binds to and sequesters β-catenin but is unable to do so when mutated, allowing β-catenin to translocate to the nucleus, where it up-regulates the expression of many genes. Around 20% of cases arise as new mutations and have no family history. Hundreds to thousands of adenomatous colonic polyps develop in 80% of patients by age 15 (Fig. 21.56), with symptoms such as rectal bleeding beginning a few years later. In those affected, cancer will develop within 10–15 years of the appearance of adenomas and 90% of patients will develop colorectal cancer by the age of 50 years. Despite surveillance, approximately 1 in 4 patients with FAP have cancer by the time they undergo colectomy. Between 10% and 20% of polyps show histological evidence of malignancy. When cancer cells are found within 2 mm of the resection margin of the polyp, when the polyp cancer is poorly differentiated or when lymphatic invasion is present, segmental colonic resection is recommended because residual tumour or lymphatic spread (in up to 10%) may be present. Malignant polyps without these features can be followed up by surveillance colonoscopy. Polyposis syndromes are classified by histopathology (Box 21.68). It is important to note that, while the hamartomatous polyps in Peutz–Jeghers syndrome and juvenile polyposis are not themselves neoplastic, these disorders are associated with an increased risk of malignancy of the breast, colon, ovary and thyroid. Familial adenomatous polyposis Familial adenomatous polyposis (FAP) is an uncommon autosomal dominant disorder affecting 1 in 13 000 of the population and Fig. 21.55 Large rectal adenomatous polyp. A Before colonoscopic polypectomy. B After polypectomy. A B 21.68 Gastrointestinal polyposis syndromes Neoplastic Non-neoplastic1 Familial adenomatous polyposis Peutz–Jeghers syndrome Juvenile polyposis Cronkhite–Canada syndrome Cowden's disease Inheritance Autosomal dominant2 Autosomal dominant Autosomal dominant in one-third None Autosomal dominant Oesophageal polyps − − − + + Gastric polyps + + + +++ +++ Small

bowel polyps ++ +++ ++ ++ ++ Colonic polyps +++ ++ ++ +++ + Other features Colorectal cancer, bleeding, extraintestinal features (see Box 21.69) Pigmentation, bleeding, intussusception, bowel and other cancers Colorectal cancer Hair loss, pigmentation, nail dystrophy, malabsorption Many congenital anomalies, oral and cutaneous hamartomas, thyroid and breast tumours − absent; + may occur; ++ common; +++ very common. 1The polyps themselves are not neoplastic but cancer risk is increased in several syndromes. 2Rare autosomal recessive variant MUTYH (see text).

age and patients who are found to have the mutation should be offered colectomy after school or college education has been completed. The operation of choice is total proctocolectomy with ileal pouch–anal anastomosis. Periodic upper gastrointestinal endoscopy every 1–3 years is recommended to detect and monitor duodenal and periampullary adenomas. If large, these may be amenable to endoscopic resection. Peutz–Jeghers syndrome Multiple hamartomatous polyps occur in the small intestine and colon, as well as melanin pigmentation of the lips, mouth and digits (Fig. 21.57). Most cases are asymptomatic, although chronic bleeding, anaemia or intussusception can occur. There is a significant risk of small bowel or colonic adenocarcinoma and of cancer of the pancreas, lung, testis, ovary, breast and endometrium. Peutz–Jeghers syndrome is an autosomal dominant disorder, most commonly resulting from truncating mutations in a serine–threonine kinase gene on chromosome 19p (STK11). Diagnosis requires two of the three following features: • small bowel polyposis • mucocutaneous pigmentation • a family history suggesting autosomal dominant inheritance. The diagnosis can be made by genetic testing but this may be inconclusive, since mutations in genes other than STK11 can cause the disorder. Affected people should undergo regular upper endoscopy, colonoscopy and small bowel and pancreatic imaging. Polyps greater than 1 cm in size should be removed. Testicular examination is essential for men, while women should undergo pelvic examination, cervical smears and regular mammography. Asymptomatic relatives of affected patients should also undergo screening. Juvenile polyposis In juvenile polyposis, tens to hundreds of mucus-filled hamartomatous polyps are found in the colorectum. One-third of cases are inherited in an autosomal dominant manner and up to one-fifth develop colorectal cancer before the age of 40. The criteria for diagnosis are: • ten or more colonic juvenile polyps • juvenile polyps elsewhere in the gut, or • any polyps in those with a family history. Germline mutations in the SMAD4 gene are often found, as are PTEN mutations. Colonoscopy with polypectomy should be performed every 1–3 years and colectomy considered for extensive involvement. A second gene involved in base excision repair (MutY homolog, MUTYH) has been identified and may give rise to colonic polyposis. MUTYH displays autosomal recessive inheritance and leads to tens to hundreds of polyps and proximal colon cancer. This variant is referred to as MUTYH-associated polyposis (MAP). Non-neoplastic cystic fundic gland polyps occur in the stomach but adenomatous polyps also arise uncommonly. Duodenal adenomas are found in over 90% and are most common around the ampulla of Vater. Malignant transformation to adenocarcinoma takes place in 10% and is the leading cause of death in those who have had prophylactic colectomy. Many extra-intestinal features are also seen in FAP (Box 21.69). Desmoid tumours occur in up to one-third of patients and usually arise in the mesentery or abdominal wall. Although benign, they may become very large, causing compression of adjacent organs, intestinal obstruction or vascular compromise, and are difficult to remove. They sometimes respond to hormonal therapy with tamoxifen, and the NSAID sulindac may bring about regression in some, by unknown mechanisms.

Congenital hypertrophy of the retinal pigment epithelium (CHRPE) occurs in some cases and is seen as dark, round, pigmented retinal lesions. When present in an at-risk individual, these are 100% predictive of the presence of FAP. A variant, Turcot's syndrome, is characterised by FAP with primary CNS tumours (astrocytoma or medulloblastoma). Early identification of affected individuals before symptoms develop is essential. The diagnosis can be excluded if sigmoidoscopy is normal. In newly diagnosed cases, genetic testing should be carried out to confirm the diagnosis and identify the causal mutation. Subsequently, all first-degree relatives should also undergo testing (p. 46). In families with known FAP, adolescents should undergo mutation testing at 13–14 years of Fig. 21.56 Familial adenomatous polyposis. There are hundreds of adenomatous polyps throughout the colon. Fig. 21.57 Peutz–Jeghers syndrome. Typical lip pigmentation. 21.69 Extra-intestinal features of familial adenomatous polyposis • Congenital hypertrophy of the retinal pigment epithelium (CHRPE, 70–80%) • Epidermoid cysts (extremities, face, scalp)* (50%) • Benign osteomas, especially skull and angle of mandible* (50–90%) • Dental abnormalities (15–25%)* • Desmoid tumours (10–15%) • Other malignancies (brain, thyroid, liver, 1–3%) *Gardner's syndrome.

 around 85% of colorectal cancers. Figure 21.59 outlines some of the common genes affected by CIN. • Microsatellite instability. This involves germline mutations in one of six genes encoding enzymes involved in repairing errors that occur normally during DNA replication (DNA mismatch repair); these genes are designated hMSH2, hMSH6, hMLH1, hMLH3, hPMS1 and hPMS2. Replication errors accumulate and can be detected in 'microsatellites' of repetitive DNA sequences. They also occur in important regulatory genes, resulting in a genetically unstable phenotype and accumulation of multiple somatic mutations throughout the genome that eventually lead to cancer. Around 15% of sporadic cancers develop this way, as do most cases of hereditary non-polyposis colon cancer (HNPCC). • CpG island methylator phenotype (CIMP). This phenotype is found in approximately 20–30% of colorectal cancers and results in widespread gene hypermethylation. The result is functional loss of tumour suppressor genes. Colorectal cancer Although relatively rare in the developing world, colorectal cancer is the second most common malignancy and the second leading cause of cancer deaths in Western countries. In the UK, the incidence is 50–60 per 100 000, equating to 30 000 cases per year. The condition becomes increasingly common over the age of 50 years. Pathophysiology Both environmental and genetic factors are important in colorectal carcinogenesis (Fig. 21.58). Environmental factors account for the wide geographical variation in incidence and the decrease in risk seen in migrants who move from high- to low-risk countries. Dietary factors are most important and these are summarised in Box 21.70; other recognised risk factors are listed in Box 21.71. Colorectal cancer development results from the accumulation of multiple genetic mutations. There are also associated epigenetic influences, such as microRNA expression signature, and potential influences from non-coding genetic variation. Currently, there are three main pathways of genetic instability and each is associated with histological, clinical and prognostic parameters: • Chromosomal instability. Mutations or deletions of portions of chromosomes arise, with loss of heterozygosity (LOH) and inactivation of specific tumour suppressor genes. In LOH, one allele of a gene is deleted but gene inactivation occurs only when a subsequent unrelated mutation affects the other allele. Chromosomal instability (CIN) occurs in Fig. 21.58 Pathogenesis of colorectal cancer (CRC). (FAP = familial adenomatous polyposis; HNPCC = hereditary non-polyposis colon cancer; JPS = juvenile polyposis syndrome; MAP = MUTYH-associated polyposis; PJS = Peutz–Jeghers syndrome) Pathogenesis of CRC Dietary risk factors Accumulation of multiple somatic mutations Single gene mutations (large effects) Multiple susceptibility genes (small effects) Sporadic CRC (~70%)

Inherited CRC (~5%) Genetic predisposition to CRC (~25%) HNPCC (Lynch syndrome I) Lynch syndrome II FAP (APC) PJS (STK11) JPS (SMAD4) MAP (MUTYH) Without polyposis With polyposis 21.70 Dietary risk factors for colorectal cancer Risk factor Comments Increased risk Red meat* High saturated fat and protein content Carcinogenic amines formed during cooking Saturated animal fat* High faecal bile acid and fatty acid levels May affect colonic prostaglandin turnover Decreased risk Dietary fibre* Effects vary with fibre type; shortened transit time, binding of bile acids and effects on bacterial flora proposed Fruit and vegetables Green vegetables contain anticarcinogens, such as flavonoids Little evidence for protection from vitamins A, C and E Calcium Binds and precipitates faecal bile acids Folic acid Reverses DNA hypomethylation Omega-3 fatty acids May be of modest benefit *Evidence is inconsistent and a clear relationship is unproven. 21.71 Non-dietary risk factors for colorectal cancer Medical conditions • Colorectal adenomas (p. 827) • Long-standing extensive ulcerative colitis or Crohn's colitis (p. 813), especially if associated with primary sclerosing cholangitis • Ureterosigmoidostomy • Acromegaly • Pelvic radiotherapy Others • Obesity and sedentary lifestyle – may be related to diet • Smoking (relative risk 1.5–3.0) • Alcohol (weak association) • Cholecystectomy (effect of bile acids in right colon) • Type 2 diabetes (hyperinsulinaemia) • Use of aspirin or NSAIDs (COX-2 inhibition) and perhaps statins associated with reduced risk (COX-2 = cyclo-oxygenase 2; NSAIDs = non-steroidal anti-inflammatory drugs)

A family history of colorectal cancer can be obtained in 20% of patients who do not fulfil the criteria for HNPCC. In these families, the lifetime risk of developing colon cancer is 1 in 12 and 1 in 6, respectively, when one or two first-degree relatives are affected. The risk is even higher if relatives were affected at an early age. The genes responsible for these cases are, however, unknown. Most colorectal cancers are 'sporadic' and arise from malignant transformation of a benign adenomatous polyp. Over 65% occur in the rectosigmoid and a further 15% occur in the caecum or ascending colon. Synchronous tumours are present in 2–5% of patients. Spread occurs through the bowel wall. Rectal cancers may invade the pelvic viscera and side walls. Lymphatic invasion is common at presentation, as is spread through both portal and systemic circulations to reach the liver and, less commonly, the lungs. Tumour stage at diagnosis is the most important determinant of prognosis (Fig. 21.60). Clinical features Symptoms vary, depending on the site of the carcinoma. In tumours of the left colon, fresh rectal bleeding is common and obstruction occurs early. Tumours of the right colon present with anaemia from occult bleeding or with altered bowel habit, but obstruction is a late feature. Colicky lower abdominal pain is present in two-thirds of patients and rectal bleeding occurs in 50%. A minority present with features of either obstruction or perforation, leading to peritonitis, localised abscess or fistula formation. Carcinoma of the rectum usually causes early bleeding, mucus discharge or a feeling of incomplete emptying. Between 10% and 20% of patients present with iron deficiency anaemia or weight loss. On examination, there may be a palpable mass, signs of anaemia or hepatomegaly from metastases. Low rectal tumours may be palpable on digital examination. With the advent of sophisticated sequencing methodologies, such as whole-exome or whole-genome sequencing, it is becoming clear that colorectal cancer displays molecular heterogeneity resulting from both common and rare genetic variants, all displaying differing levels of penetrance. About 5–10% of colon cancers are caused by HNPCC. Pedigrees with this disorder have an autosomal dominant mode of inheritance and a positive family history of colon cancer occurring at a young age. The lifetime risk in affected individuals is 80%, with a mean age at cancer development of 45 years. In contrast to sporadic colon cancer, two-thirds of tumours

occur proximally. The diagnostic criteria are listed in Box 21.72. In a subset of patients, there is also an increased incidence of cancers of the endometrium, ovary, urinary tract, stomach, pancreas, small intestine and CNS, related to inheritance of different mismatch repair gene mutations. Those who fulfil the criteria for HNPCC should be referred for pedigree assessment, genetic testing (see above) and colonoscopy. These should begin around 25 years of age or 5–10 years earlier than the youngest case of cancer in the family. Colonoscopy needs to be repeated every 1–2 years but, even then, interval cancers can still occur. Fig. 21.59 The multistep origin of cancer: molecular events implicated in colorectal carcinogenesis. (GTP = guanine triphosphate) Late adenoma Carcinoma Key gene(s) Chromosome Alteration Normal function Effect APC (adenomatous polyposis coli) 5q Truncating mutations Inhibits translocation of β-catenin to nucleus and suppresses cell growth Progression to early adenoma development K-ras 12p Gain-of-function mutations Transmembrane GTP-binding protein mediating mitogenic signals (p21) Cell proliferation DCC (deleted in colon cancer) SMAD4 18q Allelic deletion or silencing (DCC) Gain-of-function mutations (SMAD4) DCC regulates apoptosis and has a tumour suppressor function SMAD4 regulates cell growth Enhanced tumour growth, invasion and metastasis TP53 17p Allelic deletion; gain-of-function mutations Up-regulated during cell damage to arrest cell cycle and allow DNA repair or apoptosis to occur Cell proliferation; impaired apoptosis Further mutations • Anchorage independence • Protease synthesis • Telomerase synthesis • Multidrug resistance • Evasion of immune system Intermediate adenoma Early adenoma Normal *These criteria are strict and may miss some families with mutations. Hereditary non-polyposis colon cancer should also be considered in individuals with colorectal or endometrial cancer under 45 years of age. 21.72 Modified Amsterdam criteria* for hereditary non-polyposis colon cancer • Three or more relatives with colon cancer (at least one first-degree) • Colorectal cancer in two or more generations • At least one member affected under 50 years of age • Familial adenomatous polyposis excluded

 Most recurrences are within 3 years of diagnosis and affect the liver, lung, distant lymph nodes and peritoneum. Adjuvant chemotherapy with 5-fluorouracil/folinic acid or capecitabine, preferably in combination with oxaliplatin, can reduce the risk of recurrence in patients with Dukes stage C cancers and some high-risk Dukes B cancers. Post-operative radiotherapy reduces the risk of local recurrence in rectal cancer if operative resection margins are involved. Palliation of advanced disease Surgical resection of the primary tumour is appropriate for some patients with metastases to treat obstruction, bleeding or pain. Palliative chemotherapy with 5-fluorouracil/folinic acid, capecitabine, oxaliplatin or irinotecan improves survival. Patients with advanced metastatic disease may be treated with monoclonal antibodies using bevacizumab or cetuximab, either alone or together with chemotherapy. Pelvic radiotherapy is sometimes useful for distressing rectal symptoms, such as pain, bleeding or severe tenesmus. Endoscopic laser therapy or insertion of an expandable metal stent can be used to relieve obstruction (Fig. 21.61). Prevention and screening Secondary prevention aims to detect and remove lesions at an early or pre-malignant stage by screening the asymptomatic general population. Several potential methods exist: • Population-based screening of people over the age of 50 years by regular faecal occult blood (FOB) testing reduces colorectal cancer mortality and increases the proportion of early cancers detected. The sensitivity and specificity of these tests need to be improved. Traditionally, serial stool testing with or without subsequent colonoscopy is the screening method of choice in the UK. • Colonoscopy remains the gold standard and allows preventative polypectomy but is expensive, requires bowel preparation and carries risks (perforation approximately 1 : 1000). Many countries lack the resources to offer this form of screening. • Flexible sigmoidoscopy is an

alternative option and has been shown to reduce overall colorectal cancer mortality by approximately 35% (70% for cases arising in the Investigations Colonoscopy is the investigation of choice because it is more sensitive and specific than barium enema. Furthermore, lesions can be biopsied and polyps removed. Patients in whom colonoscopy is incomplete and those who are at high risk of complications can be investigated by CT colonography (virtual colonoscopy). This is a sensitive and non-invasive technique for diagnosing tumours and polyps of more than 6 mm diameter. When the diagnosis of colon cancer has been made, CT of the chest, abdomen and pelvis should be performed as a staging investigation, particularly to detect hepatic metastases. Pelvic MRI or endoanal ultrasound should be used for local staging of rectal cancer. Measurement of serum carcinoembryonic antigen (CEA) levels are of limited value in diagnosis, since values are normal in many patients, but CEA testing can be helpful during follow-up to monitor for recurrence. Management Surgery All patients should be discussed at a multidisciplinary team meeting. Those with locally advanced rectal cancer should be offered neoadjuvant radiotherapy or chemoradiotherapy to increase the subsequent chance of a complete (R0) surgical resection. A 1-week course of radiotherapy just prior to surgery reduces the risk of local recurrence in operable rectal cancer. The tumour should be removed, along with adequate resection margins and pericolic lymph nodes. Continuity should be restored by direct anastomosis, wherever possible. Carcinomas within 2 cm of the anal verge may require abdominoperineal resection and formation of a colostomy. All patients should be counselled pre-operatively about the possible need for a stoma. Total mesorectal excision reduces recurrence rates and increases survival in rectal cancer. Metastatic disease confined to liver or lung should be considered for resection, as this can be potentially curative if there is truly no disease at other sites. Post-operatively, patients should undergo colonoscopy after 6–12 months and then at 5 years to search for local recurrence or development of new lesions, which occur in 6% of cases. Adjuvant therapy About 30–40% of patients have lymph node involvement at presentation (Fig. 21.60) and are therefore at risk of recurrence. Fig. 21.60 Modified Dukes classification and survival in colorectal cancer. Prevalence at diagnosis (%) Dukes stage Definition 5-year survival rate (%) A B C D Distant metastases Tumour involving lymph nodes Extension through bowel wall Tumour confined within bowel wall

30–35

> 90

< 5

IBD and infection. Diverticular disease may be complicated by perforation, pericolic abscess, fistula formation (usually colovesical) or acute rectal bleeding. These complications are more common in patients who take NSAIDs or aspirin. After one attack of diverticulitis, the recurrence rate is around 3% per year. Over 10–30 years, perforation, obstruction or bleeding may occur, each affecting 5% of patients. Investigations Investigations are usually performed to exclude colorectal neoplasia. Diverticula can be seen during colonoscopy or on imaging modalities such as CT scan, CT colonography or barium enema (see Fig. 21.12C, p. 773). In severe diverticulosis, colonoscopy

requires expertise and carries a risk of perforation. CT is used to assess complications, such as perforation or pericolic abscess. rectosigmoid). It is recommended in the USA every 5 years in all persons over the age of 50. • Screening for high-risk patients by molecular genetic analysis is an exciting prospect but is not yet available. • CT colonography is fast and low-risk, and offers equivalent sensitivity to colonoscopy. Disadvantages include reduced sensitivity to detect polyps of less than 6 mm, the requirement for bowel preparation, exposure to ionising radiation and its inability to offer therapeutic intent. Diverticulosis Diverticula are acquired and are most common in the sigmoid and descending colon of middle-aged people. Asymptomatic diverticula (diverticulosis) are present in over 50% of people above the age of 70 years. Symptomatic diverticular disease supervenes in 10–25% of cases, while complicated diverticulosis (acute diverticulitis, pericolic abscess, bleeding, perforation or stricture) is uncommon. Pathophysiology A life-long refined diet with a relative deficiency of fibre is widely thought to be responsible and the condition is rare in populations with a high dietary fibre intake, such as in Asia, where it more often affects the right side of the colon. It is postulated that small-volume stools require high intracolonic pressures for propulsion and this leads to herniation of mucosa between the taeniae coli (Fig. 21.62). Diverticula consist of protrusions of mucosa covered by peritoneum. There is commonly hypertrophy of the circular muscle coat. Inflammation is thought to result from impaction of diverticula with faecoliths. This may resolve spontaneously or progress to cause haemorrhage, perforation, local abscess formation, fistula and peritonitis. Repeated attacks of inflammation lead to thickening of the bowel wall, narrowing of the lumen and eventual obstruction. Clinical features Symptoms are usually the result of associated constipation or spasm. Colicky pain is suprapubic or felt in the left iliac fossa. The sigmoid colon may be palpable and, in attacks of diverticulitis, there is local tenderness, guarding, rigidity (‘left-sided appendicitis’) and sometimes a palpable mass. During these episodes, there may be diarrhoea, rectal bleeding or fever. The differential diagnosis includes colorectal cancer, ischaemic colitis, Fig. 21.61 Placement of a colonic stent for an inoperable cancer with impending obstruction. A The contrast study demonstrates an obstruction. B The stent is deployed across the tumour. C A satisfactory position is demonstrated on subsequent CT scanning. A B C Fig. 21.62 The human colon in diverticulosis. The colonic wall is weak between the taeniae. The blood vessels that supply the colon pierce the circular muscle and weaken it further by forming tunnels. Diverticula usually emerge through these points of least resistance. Mesocolon Circular muscle Diverticulum Taenia (longitudinal muscle)

 Faecal impaction In faecal impaction, a large, hard mass of stool fills the rectum. This tends to occur in disabled, immobile or institutionalised patients, especially the frail elderly or those with dementia. Constipating drugs, autonomic neuropathy and painful anal conditions also contribute. Megacolon, intestinal obstruction and urinary tract infections may supervene. Perforation and bleeding from pressure-induced ulceration are occasionally seen. Treatment involves adequate hydration and careful digital disimpaction after softening the impacted stool with arachis oil enemas. Stimulants should be avoided. Melanosis coli and laxative misuse syndromes Long-term consumption of stimulant laxatives leads to accumulation of lipofuscin pigment in macrophages in the lamina propria. This imparts a brown discoloration to the colonic mucosa, often described as resembling ‘tiger skin’. The condition is benign and resolves when the laxatives are stopped. Prolonged laxative use may rarely result in megacolon or ‘cathartic colon’, in which barium enema demonstrates a featureless mucosa, loss of haustra and shortening of the bowel. Surreptitious laxative misuse is a psychiatric condition seen in young women, some of whom have a history of bulimia or anorexia nervosa (pp. 1203 and 1204). They

complain of refractory watery diarrhoea. Laxative use is usually denied and may continue, even when patients are undergoing investigation. Screening of urine for laxatives may reveal the diagnosis. Hirschsprung's disease This disease is characterised by constipation and colonic dilatation (megacolon) due to congenital absence of ganglion cells in the large intestine. The incidence is approximately 1 : 5000. About one-third of patients have a positive family history and, in these families, the disease is inherited in an autosomal dominant manner with incomplete penetrance. About 50% of familial cases and 15% of sporadic cases have mutations affecting the RET protooncogene, which is also implicated in multiple endocrine neoplasia (MEN) types 2 and 3 (also known as MEN 2a and 2b, respectively; p. 688). Unlike MEN 2 and 3, which are caused by activating RET mutations, Hirschsprung's disease is caused by loss-of-function mutations. In some kindreds, Hirschsprung's disease and MEN can actually co-segregate and this presumably represents both 'switch off' and 'switch on' of RET in different tissues. Although RET is the most important susceptibility gene, some patients with Management Diverticular disease that is asymptomatic and discovered coincidentally requires no treatment. Constipation can be relieved by a high-fibre diet, with or without a bulking laxative (ispaghula husk, 1–2 sachets daily), taken with plenty of fluids. Stimulant laxatives (see Box 21.73 below) should be avoided. Antispasmodics may sometimes help. Acute attacks of diverticulitis can be treated with antibiotics active against Gram-negative and anaerobic organisms. Severe cases require intravenous fluids, intravenous antibiotics, analgesia and nasogastric suction, but randomised trials show no benefit from acute resection compared to conservative management. Emergency surgery is reserved for severe haemorrhage or perforation. Percutaneous drainage of acute paracolic abscesses can be effective and avoids the need for emergency surgery. Patients who have repeated attacks of obstruction should undergo elective surgery once the acute episode has settled, in order to resect the affected segment of bowel with restoration of continuity by primary anastomosis. Constipation and disorders of defecation The clinical approach to patients with constipation and its aetiology have been described on page 786. Simple constipation Simple constipation is extremely common and does not signify underlying organic disease. It usually responds to increased dietary fibre or the use of bulking agents; an adequate fluid intake is also essential. Many types of laxative are available, and these are listed in Box 21.73. Severe idiopathic constipation This occurs almost exclusively in young women and often begins in childhood or adolescence. The cause is unknown but some have 'slow transit' with reduced motor activity in the colon. Others have 'obstructed defecation', resulting from inappropriate contraction of the external anal sphincter and puborectalis muscle (anismus). The condition is often resistant to treatment. Bulking agents may exacerbate symptoms but prokinetic agents or balanced solutions of polyethylene glycol '3350' benefit some patients with slow transit. Glycerol suppositories and biofeedback techniques are used for those with obstructed defecation. Others benefit from agents such as prucalopride or linaclotide. Rarely, subtotal colectomy may be necessary as a last resort. 21.74 Constipation in old age • Evaluation: particular attention should be paid to immobility, dietary fluid and fibre intake, drugs and depression. • Immobility: predisposes to constipation by increasing the colonic transit time; the longer this is, the greater the fluid absorption and the harder the stool. • Bulking agents: can make matters worse in patients with slow transit times and should be avoided. • Overflow diarrhoea: if faecal impaction develops, paradoxical overflow diarrhoea may occur. If antidiarrhoeal agents are given, the underlying impaction may worsen and result in serious complications, such as stercoral ulceration and bleeding. 21.73 Laxatives Class Examples Bulk-forming laxatives Ispaghula husk, methylcellulose Stimulants Bisacodyl, dantron (only for terminally ill patients), docusate, senna Faecal softeners Docusate, arachis oil enema Osmotic laxatives Lactulose, lactitol,

magnesium salts Others Polyethylene glycol (PEG)*, phosphate enema* *Also used for bowel preparation prior to investigation or surgery.

a high risk of perforation. Single-contrast or water-soluble barium enemas demonstrate the absence of mechanical obstruction. Management consists of treating the underlying disorder and correcting any biochemical abnormalities. The anticholinesterase neostigmine is effective in enhancing parasympathetic activity and gut motility. Decompression, with either a rectal tube or colonoscope, may be effective but needs to be repeated until the condition resolves. In severe cases, surgical or fluoroscopic defunctioning caecostomy is necessary. Anorectal disorders Faecal incontinence The normal control of anal continence is described on page 770. Common causes of incontinence are listed in Box 21.76. High-risk patients include frail older people, women after childbirth and those with severe neurological/spinal disorders, learning difficulties or cognitive impairment. Patients are often embarrassed to admit incontinence and may complain only of 'diarrhoea'. A careful history and examination, especially of the anorectum and perineum, may help to establish the underlying cause. Endoanal ultrasound is valuable for defining the integrity of the anal sphincters, while anorectal physiology and MR proctography are also useful investigations. Management This is often very difficult. Underlying disorders should be treated and diarrhoea managed with loperamide, diphenoxylate or codeine phosphate. Attention must be paid to a proper diet and adequate fluid intake. Pelvic floor exercises, biofeedback and bowel retraining techniques help some patients, and those with confirmed anal sphincter defects may benefit from sphincter repair operations. Where sphincter repair is not appropriate, a trial of sacral nerve stimulation is undertaken with a view to insertion of a permanent stimulator but, if unsuccessful, creation of a neo-sphincter may be possible, by graciloplasty or by an artificial anal sphincter. Haemorrhoids Haemorrhoids (commonly known as piles) arise from congestion of the internal and/or external venous plexuses around the anal canal. They are extremely common in adults. The aetiology is unknown, although they are associated with constipation and straining, and may develop for the first time during pregnancy. First-degree piles bleed, while second-degree piles prolapse but retract spontaneously. Third-degree piles are those that require manual replacement after prolapsing. Bright red rectal bleeding occurs after defecation. Other symptoms include pain, pruritus ani and mucus discharge; thrombosis can occur in prolapsed piles, which can be very painful (Fig. 21.63). Treatment RET mutations do not develop clinical Hirschsprung's disease, and mutations in other genes have been identified that interact to cause the disease. All of the genes implicated in Hirschsprung's disease are involved in the regulation of enteric neurogenesis, and the mutations cause failure of migration of neuroblasts into the gut wall during embryogenesis. Ganglion cells are absent from nerve plexuses, most commonly in a short segment of the rectum and/or sigmoid colon. As a result, the internal anal sphincter fails to relax. Constipation, abdominal distension and vomiting usually develop immediately after birth but a few cases do not present until childhood or adolescence. The rectum is empty on digital examination. A plain abdominal X-ray or barium enema shows a small rectum and colonic dilatation above the narrowed segment. Full-thickness biopsies are required to demonstrate nerve plexuses and confirm the absence of ganglion cells. Histochemical stains for acetylcholinesterase are also used. Anorectal manometry demonstrates failure of the rectum to relax with balloon distension. Treatment involves resection of the affected segment. Acquired megacolon This may develop in childhood as a result of voluntary withholding of stool during toilet training. In such cases, it presents after the first year of life and is

distinguished from Hirschsprung’s disease by the urge to defecate and the presence of stool in the rectum. It usually responds to osmotic laxatives. In adults, acquired megacolon has several causes. It is seen in patients with depression or dementia, either as part of the condition or as a side-effect of antidepressant drugs. Prolonged misuse of stimulant laxatives may cause degeneration of the myenteric plexus, while interruption of sensory or motor innervation may be responsible in a number of neurological disorders. Patients taking large doses of opioid analgesics can develop a megacolon: so-called ‘narcotic bowel syndrome’. Systemic sclerosis and hypothyroidism are other recognised causes. Most patients can be managed conservatively by treatment of the underlying cause, high-residue diets, laxatives and the judicious use of enemas. Prokinetics are helpful in a minority of patients. Opioid-associated constipation can be treated with the specific peripheral opioid receptor antagonist naloxegol. Subtotal colectomy is a last resort for the most severely affected patients. Acute colonic pseudo-obstruction Acute colonic pseudo-obstruction (Ogilvie’s syndrome) has many causes (Box 21.75) and is characterised by sudden onset of painless, massive enlargement of the proximal colon; there are no features of mechanical obstruction. Bowel sounds are normal or high-pitched, rather than absent. Left untreated, it may progress to perforation, peritonitis and death. Abdominal X-rays show colonic dilatation with air extending to the rectum. Caecal diameter greater than 10 cm is associated with 21.76 Causes of faecal incontinence • Obstetric trauma: childbirth, hysterectomy • Severe diarrhoea • Faecal impaction • Congenital anorectal anomalies • Anorectal disease: haemorrhoids, rectal prolapse, Crohn’s disease • Neurological disorders: spinal cord or cauda equina lesions, dementia 21.75 Causes of acute colonic pseudo-obstruction • Trauma, burns • Recent surgery • Drugs (opiates, phenothiazines) • Respiratory failure • Electrolyte and acid–base disorders • Diabetes mellitus • Uraemia

 and mucosal prolapse. The ulcer is seen at sigmoidoscopy and biopsies show a characteristic accumulation of collagen. Symptoms include minor bleeding and mucus per rectum, tenesmus and perineal pain. Treatment is often difficult but avoidance of straining at defecation is important and treatment of constipation may help. Marked mucosal prolapse is treated surgically. Anal fissure In this common problem, traumatic or ischaemic damage to the anal mucosa results in a superficial mucosal tear, most commonly in the midline posteriorly. Spasm of the internal anal sphincter exacerbates the condition. Severe pain occurs on defecation and there may be minor bleeding, mucus discharge and pruritus. The skin may be indurated and an oedematous skin tag, or ‘sentinel pile’, adjacent to the fissure is common. Avoidance of constipation with bulk-forming laxatives and increased fluid intake is important. Relaxation of the internal sphincter is normally mediated by nitric oxide, and 0.2% glyceryl trinitrate, which donates nitric oxide and improves mucosal blood flow, is effective in 60–80% of patients. Diltiazem cream (2%) can be used as an alternative. Resistant cases may respond to injection of botulinum toxin into the internal anal sphincter to induce relaxation. Manual dilatation under anaesthesia leads to long-term incontinence and should not be considered. The majority of cases can be treated without surgery, but where these measures fail, healing can be achieved surgically by lateral internal anal sphincterotomy or advancement anoplasty. Anorectal abscesses and fistulae Perianal abscesses develop between the internal and external anal sphincters and may point at the perianal skin. Ischiorectal abscesses occur lateral to the sphincters in the ischiorectal fossa. They usually result from infection of anal glands by normal intestinal bacteria. Crohn’s disease (p. 813) is sometimes responsible. Patients complain of extreme perianal pain, fever and/ or discharge of pus. Spontaneous rupture may lead to the development of fistulae. These may be superficial or track through the anal sphincters to reach the rectum. Abscesses are drained surgically and superficial

fistulae are laid open with care to avoid sphincter damage. Diseases of the peritoneal cavity Peritonitis Surgical peritonitis occurs as the result of a ruptured viscus (for details see this book's companion text, Principles and Practice of Surgery). Peritonitis may also complicate ascites in chronic liver disease (spontaneous bacterial peritonitis, p. 864) or may occur in children in the absence of ascites, due to infection with Streptococcus pneumoniae or β-haemolytic streptococci (p. 253). Chlamydial peritonitis is a complication of pelvic inflammatory disease (p. 336). The patient presents with right upper quadrant pain, pyrexia and a hepatic rub (the Fitz-Hugh–Curtis syndrome). Tuberculosis may cause peritonitis and ascites (p. 588). Tumours The most common is secondary adenocarcinoma from the ovary or gastrointestinal tract. Mesothelioma is a rare tumour complicating asbestos exposure. It presents as a diffuse involves measures to prevent constipation and straining. Band ligation is effective for many but a minority of patients require haemorrhoidectomy, which is usually curative. Haemorrhoidal artery ligation operation (HALO) procedures have been developed and may replace surgery. HALO involves using Doppler ultrasound to identify all the arteries feeding the haemorrhoids and ligating them. Pruritus ani This is common and can stem from many causes (Box 21.77), most of which result in contamination of the perianal skin with faecal contents. Itching may be severe and results in an itch–scratch–itch cycle that exacerbates the problem. When no underlying cause is found, all local barrier ointments and creams must be stopped. Good personal hygiene is essential, with careful washing after defecation. The perineal area must be kept dry and clean. Bulk-forming laxatives may reduce faecal soiling. Solitary rectal ulcer syndrome This is most common in young adults and occurs on the anterior rectal wall. It is thought to result from localised chronic trauma and/or ischaemia associated with disordered puborectalis function Fig. 21.63 Thrombosed prolapsed haemorrhoids. 21.77 Causes of pruritus ani Local anorectal conditions • Haemorrhoids • Fistula, fissures • Poor hygiene Infections • Threadworms • Candidiasis Skin disorders • Contact dermatitis • Psoriasis • Lichen planus Other • Diarrhoea or incontinence of any cause • Irritable bowel syndrome • Anxiety

B (NFκB), leading to mitochondrial dysfunction, autophagy and a vigorous inflammatory response. The normal pancreas has only a poorly developed capsule, and adjacent structures, including the common bile duct, duodenum, splenic vein and transverse colon, are commonly involved in the inflammatory process. The severity of acute pancreatitis is dependent on the balance between the activity of released proteolytic enzymes and antiproteolytic factors. The latter comprise an intracellular pancreatic trypsin inhibitor protein and circulating β2-macroglobulin, α1-antitrypsin and C1-esterase inhibitors. The causes of acute pancreatitis are listed in Box 21.80. Acute pancreatitis is often self-limiting, but in some patients with severe disease, local complications, such as necrosis, pseudocyst or abscess, occur, as well as systemic complications that lead to multi-organ failure. Clinical features The typical presentation is with severe, constant upper abdominal pain, of increasing intensity over 15–60 minutes, which radiates to the back. Nausea and vomiting are common. There is marked epigastric tenderness, but in the early stages (and in contrast to a perforated peptic ulcer), guarding and rebound tenderness are absent because the inflammation is principally retroperitoneal. Bowel sounds become quiet or absent as paralytic ileus develops. In severe cases, the patient becomes hypoxic and develops hypovolaemic shock with oliguria. Discoloration of the flanks abdominal mass, due to omental infiltration, and with ascites. The prognosis is extremely poor. Other disorders Endometriosis Ectopic endometrial tissue can become embedded on the serosal aspect of the intestine, most frequently in the sigmoid and

rectum. The overlying mucosa is usually intact. Cyclical engorgement and inflammation result in pain, bleeding, diarrhoea, constipation and adhesions or obstruction. Low backache is frequent. The onset is usually between 20 and 45 years and the condition is more common in nulliparous women. Bimanual examination may reveal tender nodules in the pouch of Douglas. Endoscopic studies reveal the diagnosis only if carried out during menstruation, when a bluish mass with intact overlying mucosa is apparent. In some patients, laparoscopy is required. Treatment options include laparoscopic diathermy and hormonal therapy with progestogens (e.g. norethisterone), gonadotrophin-releasing hormone analogues or danazol. Pneumatosis cystoides intestinalis In this rare condition, multiple gas-filled submucosal cysts line the colonic and small bowel walls. The cause is unknown but the condition may be seen in patients with chronic cardiac or pulmonary disease, pyloric obstruction, systemic sclerosis or dermatomyositis. Most patients are asymptomatic, although there may be abdominal cramp, diarrhoea, tenesmus, rectal bleeding and mucus discharge. The cysts are recognised on sigmoidoscopy, plain abdominal X-rays or barium enema. Therapies reported to be effective include prolonged high-flow oxygen, elemental diets and antibiotics. Diseases of the pancreas Acute pancreatitis Acute pancreatitis accounts for 3% of all cases of abdominal pain admitted to hospital. It affects 2–28 per 100 000 of the population and is increasing in incidence. It is a potentially serious condition with an overall mortality of 10%. About 80% of all cases are mild and have a favourable outcome. Approximately 98% of deaths from pancreatitis occur in the 20% of patients with severe disease and about one-third of these arise within the first week, usually from multi-organ failure. After this time, the majority of deaths result from sepsis, especially that complicating infected necrosis. At admission, it is possible to predict patients at risk of these complications (Box 21.78). Individuals who are predicted to have severe pancreatitis (Box 21.79) and those with necrosis or other complications should be managed in a specialist centre with an intensive care unit and multidisciplinary hepatobiliary specialists. Pathophysiology Acute pancreatitis occurs as a consequence of premature intracellular trypsinogen activation, releasing proteases that digest the pancreas and surrounding tissue. Triggers for this are many, including alcohol, gallstones and pancreatic duct obstruction (Fig. 21.64). There is simultaneous activation of nuclear factor kappa 21.79 Features that predict severe pancreatitis Initial assessment • Clinical impression of severity • Body mass index > 30 kg/m2 • Pleural effusion on chest X-ray • APACHE II score > 8 (see Box 10.50, p. 214) 24 hours after admission • Clinical impression of severity • APACHE II score > 8 • Glasgow score > 3 (see Box 21.78) • Persisting organ failure, especially if multiple • CRP > 150 mg/L 48 hours after admission • Clinical impression of severity • Glasgow score > 3 • CRP > 150 mg/L • Persisting organ failure for 48 hours • Multiple or progressive organ failure (CRP = C-reactive protein) *Severity and prognosis worsen as the number of these factors increases. More than three implies severe disease. 21.78 Glasgow criteria for prognosis in acute pancreatitis* • Age > 55 years • PO2 < 8 kPa (60 mmHg) • White blood cell count > 15 × 109/L • Albumin < 32 g/L (3.2 g/dL) • Serum calcium < 2 mmol/L (8 mg/dL) (corrected) • Glucose > 10 mmol/L (180 mg/dL) • Urea > 16 mmol/L (45 mg/dL) (after rehydration) • Alanine aminotransferase > 200 U/L • Lactate dehydrogenase > 600 U/L

 ‘pseudocysts’ are common and usually asymptomatic, resolving as the pancreatitis recovers. Pseudocysts greater than 6 cm in diameter seldom disappear spontaneously and can cause constant abdominal pain and compress or erode surrounding structures, including blood vessels, to form pseudoaneurysms. Large pseudocysts can be detected clinically as a palpable abdominal mass. Pancreatic ascites occurs when fluid leaks from a disrupted pancreatic duct into the peritoneal cavity. Leakage into the thoracic cavity can result in a pleural effusion or a

pleuro-pancreatic fistula. (Grey Turner’s sign) or the periumbilical region (Cullen’s sign) is a feature of severe pancreatitis with haemorrhage. The differential diagnosis includes a perforated viscus, acute cholecystitis and myocardial infarction. Various complications may occur and these are listed in Box 21.81. A collection of fluid and debris may develop in the lesser sac, following inflammatory rupture of the pancreatic duct; this is known as a pancreatic fluid collection. It is initially contained within a poorly defined, fragile wall of granulation tissue, which matures over a 6-week period to form a fibrous capsule (Fig. 21.65). Such Fig. 21.64 Pathophysiology of acute pancreatitis. Hyperstimulation of pancreas (alcohol, triglycerides) Pancreatic secretory trypsin inhibitors + + + + Defective intracellular transport and secretion of pancreatic zymogens Pancreatic duct obstruction (common bile duct stones, tumours) Reflux of infected bile or duodenal contents into pancreatic duct (sphincter of Oddi dysfunction) Activated proteolytic enzymes Acute pancreatitis Pro-enzymes 21.80 Causes of acute pancreatitis Common (90% of cases) • Gallstones • Alcohol • Idiopathic causes • Post-ERCP Rare • Post-surgical (abdominal, cardiopulmonary bypass) • Trauma • Drugs (azathioprine/mercaptopurine, thiazide diuretics, sodium valproate) • Metabolic (hypercalcaemia, hypertriglyceridaemia) • Pancreas divisum (p. 842) • Sphincter of Oddi dysfunction • Infection (mumps, Coxsackie virus) • Hereditary factors • Renal failure • Organ transplantation (kidney, liver) • Severe hypothermia • Petrochemical exposure (ERCP = endoscopic retrograde cholangiopancreatography) 21.81 Complications of acute pancreatitis Complication Cause Systemic Systemic inflammatory response syndrome (SIRS) Increased vascular permeability from cytokine, platelet-aggregating factor and kinin release Hypoxia Acute respiratory distress syndrome (ARDS) due to microthrombi in pulmonary vessels Hyperglycaemia Disruption of islets of Langerhans with altered insulin/glucagon release Hypocalcaemia Sequestration of calcium in fat necrosis, fall in ionised calcium Reduced serum albumin concentration Increased capillary permeability Pancreatic Necrosis Non-viable pancreatic tissue and peripancreatic tissue death; frequently infected Abscess Circumscribed collection of pus close to the pancreas and containing little or no pancreatic necrotic tissue Pseudocyst Disruption of pancreatic ducts Pancreatic ascites or pleural effusion Disruption of pancreatic ducts Gastrointestinal Upper gastrointestinal bleeding Gastric or duodenal erosions Variceal haemorrhage Splenic or portal vein thrombosis Erosion into colon Erosion by pancreatic pseudocyst Duodenal obstruction Compression by pancreatic mass Obstructive jaundice Compression of common bile duct Fig. 21.65 Computed tomogram showing large pancreatic pseudocyst (C) compressing the stomach (S). The pancreas is atrophic and calcified (arrows). S C

Management Management comprises several related steps: • establishing the diagnosis and disease severity • early resuscitation, according to whether the disease is mild or severe • detection and treatment of complications • treatment of the underlying cause. Opiate analgesics should be given to treat pain and hypovolaemia should be corrected using normal saline or other crystalloids. All severe cases should be managed in a high-dependency or intensive care unit. A central venous line and urinary catheter should be inserted to monitor patients with shock. Oxygen should be given to hypoxic patients, and those who develop systemic inflammatory response syndrome (SIRS) may require ventilatory support. Hyperglycaemia should be corrected using insulin and hypocalcaemia by intravenous calcium injection. Nasogastric aspiration is required only if paralytic ileus is present. Enteral feeding, if tolerated, should be started at an early stage in patients with severe pancreatitis because they are in a severely catabolic state and need

nutritional support. Enteral feeding decreases endotoxaemia and so may reduce systemic complications. Nasogastric feeding is just as effective as feeding by the nasojejunal route. Prophylaxis of thromboembolism with subcutaneous low-molecular-weight heparin is also advisable. The use of prophylactic, broad-spectrum intravenous antibiotics to prevent infection of pancreatic necrosis is not indicated, but infected necrosis is treated with antibiotics that penetrate necrotic tissue, e.g. carbapenems or quinolones, and metronidazole. Patients who present with cholangitis or jaundice in association with severe acute pancreatitis should undergo urgent ERCP to diagnose and treat choledocholithiasis. In less severe cases of gallstone pancreatitis, biliary imaging (using MRCP or EUS) can be carried out after the acute phase has resolved. If the liver function tests return to normal and ultrasound has not demonstrated a dilated biliary tree, laparoscopic cholecystectomy with an on-table cholangiogram is appropriate because any common bile duct stones have probably passed. When the operative cholangiogram detects residual common bile duct stones, these should be removed by laparoscopic exploration of the duct or by post-operative ERCP. Cholecystectomy should be undertaken within 2 weeks of resolution of pancreatitis – and preferably during the same admission – to prevent further potentially fatal attacks of pancreatitis. Patients with infected pancreatic necrosis or pancreatic abscess require urgent endoscopic drainage or minimally invasive retroperitoneal pancreatic (MIRP) necrosectomy to debride all cavities of necrotic material. Pancreatic pseudocysts can be treated by drainage into the stomach or duodenum. This is usually performed after an interval of at least 6 weeks, once a pseudocapsule has matured, by surgical or endoscopic cystogastrostomy. Chronic pancreatitis Chronic pancreatitis is a chronic inflammatory disease characterised by fibrosis and destruction of exocrine pancreatic tissue. Diabetes mellitus occurs in advanced cases because the islets of Langerhans are involved (p. 733). Pathophysiology Around 80% of cases in Western countries result from alcohol misuse. In southern India, severe chronic calcific pancreatitis Investigations The diagnosis is based on raised serum amylase or lipase concentrations and ultrasound or CT evidence of pancreatic swelling. Plain X-rays should be taken to exclude other diagnoses, such as perforation or obstruction, and to identify pulmonary complications. Amylase is efficiently excreted by the kidneys and concentrations may have returned to normal if measured 24–48 hours after the onset of pancreatitis. A persistently elevated serum amylase concentration suggests pseudocyst formation. Peritoneal amylase concentrations are massively elevated in pancreatic ascites. Serum amylase concentrations are also elevated (but less so) in intestinal ischaemia, perforated peptic ulcer and ruptured ovarian cyst, while the salivary isoenzyme of amylase is elevated in parotitis. If available, serum lipase measurements are preferable to amylase, as they have greater diagnostic accuracy for acute pancreatitis. Ultrasound scanning can confirm the diagnosis, although in the earlier stages the gland may not be grossly swollen. The ultrasound scan is also useful because it may show gallstones, biliary obstruction or pseudocyst formation. Contrast-enhanced pancreatic CT performed 6–10 days after admission can be useful in assessing viability of the pancreas if persisting organ failure, sepsis or clinical deterioration is present, since these features may indicate that pancreatic necrosis has occurred. Necrotising pancreatitis is associated with decreased pancreatic enhancement on CT, following intravenous injection of contrast material. The presence of gas within necrotic material (Fig. 21.66) suggests infection and impending abscess formation, in which case percutaneous aspiration of material for bacterial culture should be carried out and appropriate antibiotics prescribed. Involvement of the colon, blood vessels and other adjacent structures by the inflammatory process is best seen by CT. Certain investigations stratify the severity of acute pancreatitis and have important prognostic value at the time of presentation (see Boxes 21.78 and 21.79). In addition, serial assessment of CRP is a useful indicator of progress. A

peak CRP of > 210 mg/L in the first 4 days predicts severe acute pancreatitis with 80% accuracy. It is worth noting that the serum amylase concentration has no prognostic value. Fig. 21.66 Pancreatic necrosis. Lack of vascular enhancement of the pancreas during contrast-enhanced computed tomography indicates necrosis (arrow). The presence of gas suggests that infection has occurred.

 present with diarrhoea. Pain is due to a combination of increased pressure within the pancreatic ducts and direct involvement of peripancreatic nerves by the inflammatory process. Pain may be relieved by leaning forwards or by drinking alcohol. Approximately one-fifth of patients chronically consume opiate analgesics. Weight loss is common and results from a combination of anorexia, avoidance of food because of post-prandial pain, malabsorption and/or diabetes. Steatorrhoea occurs when more than 90% of the exocrine tissue has been destroyed; protein malabsorption develops only in the most advanced cases. Overall, 30% of patients have (secondary) diabetes but this figure rises to 70% in those with chronic calcific pancreatitis. Physical examination reveals a thin, malnourished patient with epigastric tenderness. Skin pigmentation over the abdomen and back is common and results from chronic use of a hot water bottle (erythema ab igne). Many patients have features of other alcohol- and smoking-related diseases. Complications are listed in Box 21.83. Investigations Investigations (Box 21.84 and Fig. 21.68) are carried out to: • make a diagnosis of chronic pancreatitis • define pancreatic function • demonstrate anatomical abnormalities prior to surgical intervention. occurs in non-alcoholics, possibly as a result of malnutrition, deficiency of trace elements and micronutrients, and cassava consumption. Other causes are listed in Box 21.82. The pathophysiology of chronic pancreatitis is shown in Figure 21.67. Clinical features Chronic pancreatitis predominantly affects middle-aged alcoholic men. Almost all present with abdominal pain. In 50%, this occurs as episodes of ‘acute pancreatitis’, although each attack results in a degree of permanent pancreatic damage. Relentless, slowly progressive chronic pain without acute exacerbations affects 35% of patients, while the remainder have no pain but Fig. 21.67 Pathophysiology of chronic pancreatitis. Alcohol and other risk factors may trigger acute pancreatitis through multiple mechanisms. The first (or ‘sentinel’) episode of acute pancreatitis initiates an inflammatory response involving T-helper (Th) cells. Ongoing exposure to alcohol drives further inflammation but this is modified by regulatory T cells (Treg) with subsequent fibrosis, via activation of pancreatic stellate cells. A cycle of inflammation and fibrosis ensues, with development of chronic pancreatitis. Alcohol is the most relevant risk factor, as it is involved at multiple steps. Clinical course Mechanisms Aetiology Normal Treg Th Acute pancreatitis Recurrent acute pancreatitis Recurrent acute pancreatitis Oxidative stress Alcohol Smoking Idiopathic Genetic Autoimmune Obstructive Toxic– metabolic Necrosis–fibrosis Duct obstruction Chronic pancreatitis Acinus Ductule *These can be memorised by the mnemonic ‘TIGARO’. Gallstones do not cause chronic pancreatitis but may be observed as an incidental finding. 21.82 Causes of chronic pancreatitis* Toxic–metabolic • Alcohol • Tobacco • Hypercalcaemia • Chronic kidney disease Idiopathic • Tropical • Early-/late-onset types Genetic • Hereditary pancreatitis (cationic trypsinogen mutation) • SPINK-1 mutation • Cystic fibrosis Autoimmune • In isolation or as part of multi-organ problem Recurrent and severe acute pancreatitis • Recurrent acute pancreatitis • Post-necrotic Obstructive • Ductal adenocarcinoma • Intraductal papillary mucinous neoplasia • Pancreas divisum • Sphincter of Oddi stenosis 21.83 Complications of chronic pancreatitis • Pseudocysts and pancreatic ascites, which occur in both acute and chronic pancreatitis • Obstructive jaundice due to benign stricture of the common bile duct as it passes through the diseased pancreas • Duodenal stenosis • Portal or splenic vein

thrombosis leading to segmental portal hypertension and gastric varices • Peptic ulcer

Pain relief A range of analgesic drugs, particularly NSAIDs, are valuable but the severe and unremitting nature of the pain often leads to opiate use with the risk of addiction. Analgesics, such as pregabalin and tricyclic antidepressants at a low dose, may be effective. Oral pancreatic enzyme supplements suppress pancreatic secretion and their regular use reduces analgesic consumption in some patients. Patients who are abstinent from alcohol and who have severe chronic pain that is resistant to conservative measures should be considered for surgical or endoscopic pancreatic therapy (Box 21.85). Coeliac plexus neurolysis sometimes produces long-lasting pain relief, although relapse occurs in the majority of cases. In some patients, MRCP does not show a surgically or endoscopically correctable abnormality and, in these individuals, the only surgical approach is total pancreatectomy. Unfortunately, even after this operation, some continue to experience pain. Moreover, the procedure causes diabetes, which may be difficult to control, with a high risk of hypoglycaemia (since both insulin and glucagon are absent) and significant morbidity and mortality. Malabsorption This is treated by dietary fat restriction (with supplementary medium-chain triglyceride therapy in malnourished patients) and oral pancreatic enzyme supplements. A PPI is added to optimise duodenal pH for pancreatic enzyme activity. Management of complications Surgical or endoscopic therapy may be necessary for the management of pseudocysts, pancreatic ascites, common bile duct or duodenal stricture and the consequences of portal hypertension. Many patients with chronic pancreatitis also require treatment for other alcohol- and smoking-related diseases and for the consequences of self-neglect and malnutrition. Autoimmune pancreatitis Autoimmune pancreatitis (AIP) is a form of chronic pancreatitis that can mimic cancer but which responds to glucocorticoids. It is characterised by abdominal pain, weight loss or obstructive jaundice, without acute attacks of pancreatitis. Blood tests reveal increased serum IgG or IgG4 and the presence of other autoantibodies. Imaging shows a diffusely enlarged pancreas, narrowing of the pancreatic duct and stricturing of the lower bile duct. AIP may occur alone or with other autoimmune disorders, such as Sjögren’s syndrome, primary sclerosing cholangitis or IBD. The response to glucocorticoids is usually excellent but some patients require azathioprine. Management Alcohol misuse Alcohol avoidance is crucial in halting progression of the disease and reducing pain. Fig. 21.68 Imaging in chronic pancreatitis. A Computed tomogram showing a grossly dilated and irregular duct with a calcified stone (arrow A). Note the calcification in the head of the gland (arrow B). B Magnetic resonance cholangiopancreatogram of the same patient showing marked ductal dilatation with abnormal dilated side branches (arrows A). A small cyst is also present (arrow B). A B A B A B 21.84 Investigations in chronic pancreatitis Tests to establish the diagnosis • Ultrasound • Computed tomography (may show atrophy, calcification or ductal dilatation) • Abdominal X-ray (may show calcification) • Magnetic resonance cholangiopancreatography • Endoscopic ultrasound Tests to define pancreatic function • Collection of pure pancreatic juice after secretin injection (gold standard but invasive and seldom used) • Pancreolauryl test (see Box 21.12, p. 777) • Faecal pancreatic elastase Tests to demonstrate anatomy prior to surgery • Magnetic resonance cholangiopancreatography 21.85 Intervention in chronic pancreatitis Endoscopic therapy • Dilatation or stenting of pancreatic duct strictures • Removal of calculi (mechanical or shock-wave lithotripsy) • Drainage of pseudocysts Surgical methods • Partial pancreatic resection, preserving the duodenum • Pancreatico-jejunostomy

842 • GASTROENTEROLOGY as often as women. The disease is associated with increasing age, smoking and chronic pancreatitis. Between 5% and 10% of patients have a genetic predisposition: hereditary pancreatitis, HNPCC and familial atypical mole multiple melanoma syndrome (FAMMM). Overall survival is only 3–5%, with a median survival of 6–10 months for those with locally advanced disease and 3–5 months if metastases are present. Clinical features Many patients are asymptomatic until an advanced stage, when they present with central abdominal pain, weight loss and obstructive jaundice (Fig. 21.69). The pain results from invasion of the coeliac plexus and is characteristically incessant and gnawing. It often radiates from the upper abdomen through to the back and may be eased a little by bending forwards. Almost all patients lose weight and many are cachectic. Around 60% of tumours arise from the head of the pancreas, and involvement of the common bile duct results in the development of obstructive jaundice, often with severe pruritus. A few patients present with diarrhoea, vomiting from duodenal obstruction, diabetes mellitus, recurrent venous thrombosis, acute pancreatitis or depression. Physical examination reveals clear evidence of weight loss. An abdominal mass due to the tumour itself, a palpable gallbladder or hepatic metastasis is commonly found. A palpable gallbladder in a jaundiced patient is usually the consequence of distal biliary obstruction by a pancreatic cancer (Courvoisier’s sign). Investigations The diagnosis is usually made by ultrasound and contrastenhanced CT (Fig. 21.70). Diagnosis in non-jaundiced patients is often delayed because presenting symptoms are relatively non-specific. Fit patients with small, localised tumours should undergo staging to define operability. EUS or laparoscopy with laparoscopic ultrasound will define tumour size, involvement of blood vessels and metastatic spread. In patients unsuitable for surgery because of advanced disease, frailty or comorbidity, EUS- or CT-guided cytology or biopsy can be used to confirm the diagnosis (Fig. 21.70). MRCP and ERCP are sensitive methods of diagnosing pancreatic cancer and are valuable when the diagnosis is in doubt, although differentiation between cancer and localised chronic pancreatitis can be difficult. The main role of ERCP is to insert a stent into the common bile duct to relieve obstructive jaundice in inoperable patients. Management Surgical resection is the only method of effecting cure, and 5-year survival in patients undergoing a complete resection is around 12%. Clinical trials have demonstrated improved survival (21–29%) with adjuvant chemotherapy using gemcitabine. Unfortunately, only 10–15% of tumours are resectable for cure, since most are locally advanced at the time of diagnosis. For the great majority of patients, treatment is palliative. Chemotherapy with FOLFIRINOX (5-fluorouracil, leucovorin, irinotecan and oxaliplatin) improves median survival to 11 months. Pain relief can be achieved using analgesics but, in some patients, coeliac plexus neurolysis may be required. Jaundice can be relieved by choledochojejunostomy in fit patients, whereas percutaneous or endoscopic stenting is preferable in the elderly and those with very advanced disease. Ampullary or periampullary adenocarcinomas are rare neoplasms that arise from the ampulla of Vater or adjacent duodenum. They are often polypoid and may ulcerate; they frequently infiltrate the duodenum but behave less aggressively than pancreatic adenocarcinoma. Around 25% of patients undergoing resection Congenital abnormalities affecting the pancreas Pancreas divisum This is due to failure of the primitive dorsal and ventral ducts to fuse during embryonic development of the pancreas. As a consequence, most of the pancreatic drainage occurs through the smaller accessory ampulla rather than through the major ampulla. The condition occurs in 7–10% of the normal population and is usually asymptomatic, but some patients develop acute pancreatitis, chronic pancreatitis or atypical abdominal pain. Annular pancreas In this congenital anomaly, the pancreas encircles the second/third part of the duodenum, leading to gastric outlet obstruction. Annular pancreas is associated with malrotation of the intestine, atresias and cardiac anomalies. Cystic fibrosis This disease is

considered in detail on page 580. The major gastrointestinal manifestations are pancreatic insufficiency and meconium ileus. Peptic ulcer and hepatobiliary disease may also occur. In cystic fibrosis, pancreatic secretions are protein- and mucus-rich. The resultant viscous juice forms plugs that obstruct the pancreatic ductules, leading to progressive destruction of acinar cells. Steatorrhoea is universal and the large-volume bulky stools predispose to rectal prolapse. Malnutrition is compounded by the metabolic demands of respiratory failure and by diabetes, which develops in 40% of patients by adolescence. Nutritional counselling and supervision are important to ensure intake of high-energy foods, providing 120–150% of the recommended intake for normal subjects. Fats are an important calorie source and, despite the presence of steatorrhoea, fat intake should not be restricted. Supplementary fat-soluble vitamins are also necessary. High-dose oral pancreatic enzymes are required, in doses sufficient to control steatorrhoea and stool frequency. A PPI aids fat digestion by producing an optimal duodenal pH. Meconium ileus Mucus-rich plugs within intestinal contents can obstruct the small or large intestine of a newborn child. Meconium ileus is treated by the mucolytic agent N-acetylcysteine, given either orally, by Gastrografin enema or by gut lavage using polyethylene glycol. In resistant cases of meconium ileus, surgical resection may be necessary. Tumours of the pancreas Adenocarcinoma of the pancreas Some 90% of pancreatic neoplasms are adenocarcinomas that arise from the pancreatic ducts. These tumours involve local structures and metastasise to regional lymph nodes at an early stage. Most patients have advanced disease at the time of presentation. Neuro-endocrine tumours also arise in the pancreas but tend to grow more slowly and have a better prognosis; these are discussed in detail on page 678. Pancreatic adenocarcinoma affects 10–15 per 100 000 in Western populations, rising to 100 per 100 000 in those over the age of 70. Men are affected twice

Fig. 21.69 Features of pancreatic cancer. Lymphadenopathy Pancreatic tumour mass Sister Joseph’s nodule (tumour spread to umbilicus via umbilical vein) Erythema ab igne Venous thrombosis (‘thrombophlebitis migrans’) Metastases common Obstructed common bile duct and dilated gallbladder Cancer Dilated pancreatic duct Lymph node spread at early stage Jaundice Cachexia Depression Vomiting from duodenal obstruction Hepatomegaly (extrahepatic biliary obstruction/secondary deposits) Palpable gallbladder (Courvoisier’s sign) Scratch marks (obstructive jaundice) Fig. 21.70 Carcinoma of the pancreas. A A computed tomogram showing a large, necrotic mass encasing the coeliac axis (arrows). B Endoscopic ultrasound was subsequently performed to enhance staging and to obtain a fine needle aspiration biopsy, which confirmed pancreatic ductal adenocarcinoma. A B

 or to monitor depends on age and fitness of the patient and location, size and evolution of lesions. Further information Books and journal articles Canard JM, Letard J-C, Palazzo L, et al. Gastrointestinal endoscopy in practice. Edinburgh: Churchill Livingstone; 2011. Feldman M, Friedman LS, Brandt LJ. Sleisenger and Fordtran’s Gastrointestinal and liver disease, 10th edn. Philadelphia: Elsevier Saunders; 2015. Websites bsg.org.uk British Society of Gastroenterology. crohnsandcolitis.org.uk Crohn’s and Colitis UK. coeliac.org.uk Coeliac UK. ecco-ibd.eu European Crohn’s and Colitis Organisation. gastro.org American Gastroenterological Association and American Digestive Health Foundation. isg.org.in Indian Society of Gastroenterology. of ampullary or periampullary tumours survive for 5 years, in contrast to patients with pancreatic ductal cancer. Incidental pancreatic mass Cystic neoplasms of the pancreas are increasingly being seen with widespread use of CT. These are a heterogeneous group; serous

cystadenomas rarely, if ever, become malignant and do not require surgery. Mucinous cysts occur more often in women, are usually in the pancreatic tail and display a spectrum of behaviour from benign to frankly malignant. Aspiration of the cyst contents for cytology and measurement of CEA and amylase concentrations in fluid obtained at EUS can help determine whether a lesion is mucinous or not. In fit patients, all mucinous lesions should be resected. A variant, called intraductal papillary mucinous neoplasia (IPMN), is often discovered coincidentally on CT, frequently in elderly men. This may affect the main pancreatic duct with marked dilatation and plugs of mucus, or may involve a side branch. The histology varies from villous adenomatous change to dysplasia or carcinoma. Since IPMN is a pre-malignant but indolent condition, the decision to resect

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