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DISORDERS OF THE GASTROINTESTINAL TRACT, PANCREAS, LIVER AND GALL BLADDER

OBJECTIVES

After studying this chapter you should be able to:

- outline the structure of the gastrointestinal tract and its accessory organs;
- describe the processes involved in the digestion of foods;
- outline the process whereby nutrients are absorbed by the gastrointestinal tract;
- review the role of the small intestine in homeostasis;
- explain the causes of some pancreatic, liver and gall bladder disorders;
- describe some common gastrointestinal tract disorders.

11.1 INTRODUCTION

The gastrointestinal tract (GIT) is essentially a long tube extending from the mouth to the anus with a number of specialized regions. Most of the nutrients (*Chapter 10*) in food have to be digested before they can be assimilated. Digestion involves the hydrolysis of polysaccharides, oligosaccharides, proteins and lipids in enzyme-catalyzed reactions. The products of hydrolysis, such as monosaccharides, amino acids, free fatty acids and monoacylglycerols, can then be absorbed. Some nutrients, vitamins and minerals for instance, are absorbed without the need for digestion. The digestion of food and absorption of the released nutrients are the major functions of the GIT together with its accessory organs, the pancreas, liver and gall bladder. The peritoneum lines the abdominal cavity and covers the major organs. Folds of the peritoneum, called the mesentery, and mesocolon hold the intestines in place. The GIT has significant roles in the homeostasis of nutrients and in protecting the body against pathogens (Chapter 2) ingested with the food. Digestion and absorption, can, of course, only take place after ingestion of food, unlike the homeostatic and protective functions that operate continuously.

11.2 THE GASTROINTESTINAL TRACT AND ITS ACCESSORY ORGANS

The GIT may be described as a tubular system with distinctive regions that begin with the mouth leading to the pharynx, esophagus, stomach, the small and large intestines and terminating at the anus (Figure 11.1 (A)). It is associated with several accessory digestive organs, such as the pancreas, liver and gall bladder (Figure 11.1 (B)). The walls of the GIT have a fairly common substructure (Figure 11.2 (A) and (B)) and its interior is called the lumen. The GIT and accessory organs are bound to each other and to the inner wall of the abdomen by the **peritoneum**. This is a strong, colorless membrane with a smooth surface that consists of two parts; the parietal peritoneum, which lines the abdominal cavity, and the visceral peritoneum that covers most of the organs in the abdomen (*Figure 11.3*). The thin space between the two parts, called the peritoneal cavity, is filled with serous fluid. In males, the peritoneum forms a closed sac but in females it is continuous with the mucous membrane of the uterine tubes. The **mesentery** is a fan shaped portion of peritoneum that extends from the posterior abdominal wall and wraps around the small intestine and returns to its origin forming a double layer (Figure 11.4). The mesentery contains the blood and





Figure 11.2 Outline of the tissue organization of the walls of (A) the stomach and (B) the small intestine.



Figure 11.3 Schematic showing the peritoneum.

lymphatic vessels and nerves that supply the small intestine. Another peritoneal fold, the **mesocolon** (*Figure 11.4*), has similar functions with respect to the large intestine. The mesentery and mesocolon anchor the intestines in place but only loosely, allowing them considerable movement as muscular activities mix and move the contents through the GIT.

The pancreas is found near the stomach and small intestine (*Figure 11.1 (A*) and (*B*)) and functions as both an exocrine and an endocrine gland. In its exocrine role it produces pancreatic juice that is released into the first part of the small intestine, the duodenum, through the pancreatic duct. This secretion contains precursors of digestive enzymes that are activated and function in the GIT, and also hydrogen carbonate (HCO₃) that increases the pH of GIT contents. This latter function is vital since the material leaving the stomach is acidic. The pancreas produces about 1200–1500 cm³ of pancreatic juice per





day. Within the tissues of the pancreas are groups of cells called the islets of Langerhans. The cells in the islets have endocrine functions and produce and secrete the peptide hormones glucagon and insulin that regulate the concentration of glucose in the blood (*Chapter 7*).

The liver is the largest organ in the body (*Figure 11.1 (A*) and (*B*)), weighing about 1.5 kg. It has two major lobes, each divided into functional units called lobules. Lobules consist of cuboidal cells arranged around a central vein into which the blood drains. Between the plates of hepatic cells are sinusoids that are supplied by the portal vein and hepatic artery (*Figure 12.2* and *Chapter 12*). The sinusoids are lined with phagocytic Kupffer cells that belong to the

BOX 11.1 Peritonitis

Peritonitis is an inflammation of the peritoneum that lines the abdominal cavity and covers the surfaces of abdominal organs. The condition is marked by exudations into the peritoneum of serum, fibrin, cells and pus. Primary peritonitis is caused by the spread of an infection from the blood and lymph nodes to the peritoneum and accounts for less than 1% of all cases. Secondary peritonitis is the commonest type and occurs when bacteria enter the peritoneum from the GIT or biliary tract. The symptoms of peritonitis may include vomiting, swelling of the abdomen, severe abdominal pain and tenderness, weight loss, constipation and moderate fever. Its major causes are perforations of GIT wall, which allows seepage of the luminal contents into the abdominal cavity. These can arise from a ruptured appendix or from perforations of the stomach, including damage from ulcers, and gall bladder. Pelvic inflammatory disease in sexually active women is also a common cause. Peritonitis can also develop after surgery when bacteria have been allowed to enter the abdomen during an operation.

Peritonitis must be rapidly diagnosed and treated because complications can occur rapidly. Diagnosis relies on taking a medi-

cal history and a physical examination, particularly to investigate any abdominal swelling and tenderness. Diagnostic tests include using X-rays or a CT scan (Chapter 18) of the abdomen to confirm the presence of fluid, accumulation of pus or infected organs in the abdomen. Microbiological tests on samples of blood or abdominal fluid can identify the causative microorganism. Peritonitis is frequently life-threatening and acute peritonitis is a medical emergency. The outlook for untreated patients is poor. Specific treatments for peritonitis depend on the age, health, medical history and the severity of the condition. Treatment is generally aimed at treating the underlying condition. Antibiotics are given immediately once peritonitis has been diagnosed. A nasal tube may be inserted into the stomach or intestine to drain fluid and gas. Peritoneal lavage, where large amounts of fluid are injected into the peritoneum to wash out the infective microorganisms causing the condition, may be desirable. Intravenous fluids are also given to replace lost body fluids. Morphine may be prescribed in hospitalized patients to reduce pain. Emergency exploratory surgery may be necessary, especially in cases that involve appendicitis, a perforated peptic ulcer or diverticulitis.

reticuloendothelial system and their main function is to engulf bacteria and other foreign particles in blood. Thus there is a dual blood supply to liver, with blood coming from the digestive tract and spleen through the portal vein, and from the aorta in the hepatic artery (*Figure 14.2*). About a third of incoming blood is arterial, and brings oxygen, whereas two thirds is venous from the portal vein.

The large reserve capacity of the liver means that it needs only 10–20% of its tissues to be functioning to sustain life. It also has a remarkable ability to regenerate itself after its tissue has been removed or destroyed by disease. Complete destruction or removal of the liver results in death within 10 h, hence liver disease with loss of function is a serious matter (Chapter 12). The liver has numerous functions. It acts as an interface between the GIT and the rest of the body tissues because the hepatic portal vein carries blood directly to it from the GIT. Hence it is able to regulate the posthepatic blood concentrations of many of the nutrients absorbed by the GIT. Similarly, the liver also regulates the concentrations of many biomolecules produced by the body, for example steroid hormones, and deals with many toxins, such as drugs, pesticides and carcinogens, to render them less harmful and solubilizes them for excretion (*Chapter 12*). The liver also produces many of the plasma proteins including albumin and the clotting factors (*Chapter 13*). Bile produced by the hepatocytes is secreted into bile canaliculi and eventually drains into the bile duct. About 700–1200 cm³ of bile are produced daily and stored and concentrated in a hollow organ called the gall bladder (Figure 11.1 (A) and (B)) prior to its release in the small intestine. Bile does not contain enzymes, but it does contain bile salts, for example sodium glycocholate and taurocholate. These are detergents that aid in the digestion of lipids by emulsifying them to form water-soluble complexes.

Bile pigments are derived from heme which results from the destruction of old erythrocytes (Chapter 13). In the spleen (Figure 11.1 (A) and (B)), destruction of red blood cells releases hemoglobin, which is then catabolized to free heme and globin. The latter is degraded to amino acids. Bilirubin is derived from heme, the iron-containing protoporphyrin ring of hemoglobin. A typical adult produces around 450 µmol of bilirubin per day. This bilirubin is referred to as unconjugated bilirubin. It is insoluble in water and is transported in the plasma bound to albumin to be taken up by hepatocytes. Here, it is conjugated with glucuronic acid by UDPglucuronyltransferase to form mono- and diglucuronides in a manner resembling the detoxification reactions described in Chapter 12. Conjugated bilirubin is much more water soluble than its unconjugated form and is secreted into the bile duct. In the small intestine, conjugated bilirubin is a substrate for bacteria that convert it to urobilinogen and stercobilin. Most stercobilin is excreted in feces, although some urobilinogen is absorbed and taken to the liver in the hepatic portal vein and re-excreted in bile or by the kidneys (Figure 11.5).

11.3 DIGESTION

Digestion is the hydrolytic breakdown of nutrient macromolecules and compound lipids to smaller products that can be absorbed. The hydrolytic reactions are catalyzed by a variety of enzymes: proteases that digest proteins; carbohydrases that digest carbohydrates; lipases that catalyze the hydrolysis of lipids and nucleases that degrade DNA and RNA. Digestion occurs in the mouth, to a small extent, stomach and small intestine, and most absorption of nutrients occurs in the small intestine and that of water in the large intestine.

Margin Note 11.1 Flavor and taste

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Flavor is a complicated amalgam of sensory perceptions, involving the taste, smell and texture of foods, previous exposure to particular foods, especially in childhood, and even the noises associated with chewing some foods. In general, much of the everyday sensation of flavor is derived largely from olfactory stimulation. **Anosmia**, the loss of the sense of smell, for example when infected with a cold, can severely reduce the sense of taste.

Six tastes can be detected by different types of sensory taste buds distributed over the tongue. These are bitter, salty, sour, sweet, fats (fatty acids) and savory or umami. The first four are self-explanatory. The perception of fats is more strictly the detection of small amounts of fatty acids hydrolyzed from lipids by the action of lingual lipase. In 1907, Ikeda working at the Tokyo Imperial University investigated the source of a flavor well recognized in many Asian countries called umami. This most easily translates in English as savory or meaty. He was successful in extracting crystals of the amino acid, glutamate from a type of seaweed called kombu used in traditional Japanese cuisine. Many foods that have a umami flavor are protein rich, for example meat, seafoods, aged cheeses, and contain large amounts of glutamate. Monosodium glutamate (MSG) was developed as a food additive and is probably the most familiar example of an additive that imparts a savory or umami taste.

The evolution of specific taste receptors is most easily explained by the advantages gained in detecting foods rich in essential nutrients (salty, sweet, fats and savory) and in avoiding ones that contain toxins (bitter and sour).



Figure 11.5 Overview of the production and excretion of bilirubin following the catabolism of heme. See text for details.

MOUTH

In the mouth, teeth break the food into smaller portions increasing the surface area upon which digestive enzymes can act. Three pairs of salivary glands, the submandibular located under the jaws, the sublingual located under the tongue and the parotid situated in front of the ears (*Figure 11.6*), secrete saliva into the mouth. The saliva contains amylase (*Figure 11.7*), water and mucus. The water helps to dissolve nutrients, while the mucus acts as a lubricant to aid swallowing and lubricates passage of food through the GIT. Chewing and the actions of the tongue mix the food with the saliva. Salivary amylase begins the digestion of carbohydrates (*Figure 11.8*) although the digestion of carbohydrates in the mouth is minimal since the food is not retained there for any length of time. Lingual lipase is secreted by lingual serous glands. Again, little digestion occurs in the mouth but it has been suggested that the fatty acids

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Figure 11.7 Molecular model of a salivary amylase molecule. PDB file 1SMD.

released by its action are perceived by specific taste receptors allowing fatty foods, and therefore energy rich nutrients, to be detected.

In swallowing, the soft palate is elevated, which seals off the nasal cavity and pushes against the back wall of the pharynx. This, in turn, triggers an automatic reflex action in muscles that raise the larynx, pushing its opening, the glottis, against a flap of tissue called the epiglottis. These actions prevent food entering the trachea of the respiratory system and ensure food is expelled from the mouth into the esophagus. Rhythmic waves of contraction of smooth muscle tissue in the walls of the GIT, called **peristalsis**, forces food along the GIT. Peristalsis in the esophagus ensures that food is propelled to the stomach even if the person is upside down.



Figure 11.8 Schematic outlining the digestion (hydrolysis) of carbohydrates (polysaccharide).

STOMACH

The stomach is a sac-like region of the GIT (*Figure 11.1* (*A*) and (*B*)). Its inner surface is highly folded (*Figure 11.9*) allowing it to expand up to eightfold from its empty volume of about 50 cm³ following a meal. Muscular activities of the stomach wall mix the food with gastric juice secreted by gastric glands located in the mucosal lining of the stomach. Gastric glands produce about 1 to 2 dm³

Margin Note 11.2 Gastric lipase and cystic fibrosis

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Patients suffering cystic fibrosis (CF, Chapter 15) are defective in pancreatic lipase and other enzyme activities due to exocrine pancreatic insufficiency when the pancreatic duct becomes blocked with a thick secretion. This reduces their ability to digest lipids and leads to lipid malabsorption and steatorrhea (Section 11.8). Many CF patients are treated with supplements of porcine pancreatic extracts that contain pancreatic lipase activity. However, these supplements are needed in high doses because the duodenums of many cystic fibrosis patients are more acidic than in healthy individuals and denaturation or inhibition of the enzyme can occur. The treatment is effective in only 30% of cystic fibrosis patients and 15-20% still suffer from steatorrhea. There is considerable interest in using recombinant mammalian gastric lipases since these are resistant to acid damage and inhibition and so should prove a more effective treatment.



Figure 11.10 Molecular model of a pepsin molecule. PDB file 1QRP.

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Figure 11.9 The major regions of the stomach.

of gastric juice per day from three types of secretory cells. Parietal or oxyntic cells produce hydrochloric acid (HCl), peptic or chief cells secrete pepsinogen, the precursor of pepsin, and gastric lipase, and mucous cells that secrete mucus that protects the mucosa lining the stomach from the corrosive action of the HCl.

The activity of salivary amylase continues within the bolus and is possibly only inactivated when the bolus contents are completely mixed with the acidic gastric juice. The pH optimum of lingual lipase is between 3.5 and 6.0 and is activated in the upper portion of the stomach. Gastric lipase is secreted by the chief cells of the stomach and also has an acid optimum. About 10 to 30% of dietary fat may be hydrolyzed in the stomach. However, lipase activity in the stomach is highest against triacylglycerols with short or medium length fatty acid residues, which are found in milk, and so may be of most importance in newborn infants.

Pepsinogen is a weakly-active protease. It has an acid optimum pH, hence the need for HCl secretion in the stomach. In these conditions, about pH 1 to 2, protein molecules in the food are denatured making them more susceptible to digestion. Also, at this pH, pepsinogen molecules act on one another at specific sites to produce the fully active protease, pepsin (*Figure 11.10*), that begins the digestion of the denatured proteins to form shorter polypeptides and peptides. The denaturation and digestion of proteins reduces the chance of their absorption and prevents them being immunogenic (*Chapter 4*). The watery mixture of gastric juice and partially digested food is called **chyme**.

The acid also activates intrinsic factor (IF), a glycoprotein secreted by the parietal cells that is needed for absorption of vitamin B_{12} (*Chapter 13*). Vitamin B_{12} is released from dietary proteins by the action of pepsin and binds to one of two binding proteins present in gastric juice whose affinity for vitamin B_{12} is increased in acid conditions and is greater than that of IE. When chyme enters the small intestine, proteases from pancreatic juice break down the binding proteins and vitamin B_{12} becomes bound to IF. The mucosal lining in the ileum has receptors for IF which bind the IF–vitamin B_{12} complex, so that vitamin B_{12} is absorbed and enters the portal blood. Given that the absorption of vitamin B_{12} is dependent upon IF, any condition that decreases the secretion of IF, for example atrophic gastritis (*Section 11.8*), interferes with digestion of the binding proteins, for example pancreatic exocrine insufficiency, or decreases the binding and internalization of the IF–vitamin B_{12} complex, such as some diseases that affect the ileum, can cause pernicious anemia (*Chapter 13*).

The acid environment of the stomach kills most of the bacteria that are ingested with the food but some survive and enter the small intestine in the

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chyme. The pyloric sphincter controls the passage of chyme from the stomach to the small intestine allowing only relatively small amounts of chyme through at any one time. This control is necessary because the digestive activity within the small intestine is time-consuming and because its capacity is limited. The activities of the stomach and small intestine are coordinated by the nervous and endocrine systems.

SMALL INTESTINE

The final stages of digestion and the absorption of its products occur in the small intestine (*Figure 11.1* (*A*)). Contractions in the small intestine help to break food up, mix it with digestive juices and propel it towards the colon. The small intestine is about 23 feet (7 m) long in an adult. It is divided into three sections: the duodenum constitutes the first 250 mm, followed by the jejunum then the ileum. Digestion occurs primarily in the duodenum and jejunum and absorption in the ileum.

The walls of the duodenum contain goblet cells that secrete mucus that protects it against damage by acidic chyme. Crypts of Lieberkuhn are pits within the wall of the small intestine with secretory cells that release intestinal juice and Paneth cells that secrete lysozyme. Intestinal juice is largely water with mucus and buffered to a pH of about 7.6. Along with pancreatic juice (*see below*), it neutralizes chyme and provides a liquid medium that aids absorption of nutrients. Lysozyme is an antibacterial enzyme. The epithelial lining consists of cells called enterocytes organized into small projections into the lumen called villi (*Figure 11.11*). In turn, each enterocyte



Disaccharides, as their name implies, are composed of two simple sugars (monosaccharide residues) covalently bound together by a glycosidic bond. A variety of disaccharides are known, which can be found naturally or produced by the action of digestive enzymes on polysaccharides. Disaccharides differ from one another in the nature of their constituent monosaccharides and the type of glycosidic bond joining them together (*Table 11.1*).



Figure 11.11 A villus with its associated crypts of Lieberkuhn.

BOX 11.2 Cyclic vomiting syndrome

Vomiting or **emesis** is the expulsion of food from the stomach (and sometimes duodenum) through the esophagus and mouth. It is usually experienced as the final of three events, nausea, retching and vomition. Nausea is an unpleasant psychic experience associated with decreased gastric motility and increased muscle tone in the small intestine. Additionally, there is often reverse peristalsis in the proximal small intestine. Retching or dry heaves is the spasmodic respiratory movements conducted with a closed glottis. While this is occurring, the antrum of the stomach contracts and the fundus and cardia relax. Vomition is when the contents of the stomach and sometimes small intestine are propelled up to and out of the mouth.

Vomiting can be initiated by a variety of stimuli, including infections (gastroenteritis), various chemical irritants (emetics) and poisons, distension of the stomach, unpleasant sights and smells, dizziness, anesthetics, a number of drugs, a variety of illnesses, for example brain tumors, and hormonal changes associated with pregnancy. All result in nervous impulses being sent to a vomiting center in the medulla oblongata, which responds by sending motor impulse to muscles of the upper GIT, diaphragm and abdominal muscles (Figure 11.12). The resulting contractions squeeze the stomach between the diaphragm and abdominal muscles and expel its contents. A simple episode of vomiting rarely causes problems but may on occasion have more serious consequences, such as aspiration pneumonia. However, severe or repetitive vomiting results in disturbances to acid–base balance, electrolyte depletion and dehydration. In such cases, the underlying cause must be rapidly identified and appropriate therapy initiated. In many cases antiemetic drugs must be administered to suppress vomiting and reduce its sequelae.

Cyclic vomiting syndrome (CVS) or abdominal migraine is a disorder of the GIT characterized by recurrent, severe and pro-

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Figure 11.12 The site of the vomiting center in the medulla oblongata.

longed attacks of nausea, vomiting and abdominal pain that was first described by Gee in 1882. It usually occurs in children of two to 16 years old, most commonly between the ages of three and seven years, but can also occur in adults. The cause of CVS is unknown. Its incidence and prevalence is also uncertain but some evidence suggests that 1 in 50 children in the USA may be affected.

Margin Note 11.4 Zymogens

Digestive enzymes are produced as inactive precursors called zymogens (*Table 11.2*), which ensures the protection of the cells and tissues that produce them from the catalytic activities of the enzymes. Activation is achieved by a partial and specific hydrolysis of part of the zymogen structure that masks the active site. has its apical plasma membrane surface, which is the side facing the lumen of the GIT, arranged into microscopic extensions called microvilli forming a **brush border** that coats the villi (*Figure 11.13*). The opposing face of the enterocyte is called the basolateral membrane. The presence of villi and microvilli means that the interior surface area of the small intestine is enormous, estimated at 300 m² in humans. Hydrolytic enzymes that are integral proteins of the plasma membranes forming the microvilli catalyze further digestive reactions. For example: lactose is hydrolyzed to glucose and galactose in a reaction catalyzed by lactase; sucrose to glucose and fructose by sucrase; and the disaccharides maltose and isomaltose, produced by the action of amylase on starch, are hydrolyzed to glucose by maltase and isomaltase activities (*Table 11.1*).

Pancreatic juice is produced by the pancreas and contains water, alkaline salts that give it a pH of 7.8 to 8.0, enzymes and zymogens (*Margin Note 11.4*) and

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Cyclic vomiting syndrome occurs in four distinct phases. First, there is a prodrome phase, which is often accompanied by abdominal pain, and which signals that an episode of nausea and vomiting is about to begin. This can last a few minutes to several hours. However, sometimes a prodrome does not occur and patients enter the second phase, an episode, directly. Episodes consist of nausea followed by severe vomiting, which usually begin at night or first thing in the morning. Abdominal pain, dizziness, headaches, photosensitivity, fever and sometimes diarrhea may also present. Vomiting can

ing. Abdominal pain, dizziness, headaches, photosensitivity, fever and sometimes diarrhea may also present. Vomiting can be as frequent as six to 12 times an hour during the worst of the episode and can continue for one to five days during which the patient appears pale, listless and exhausted, often to the point of near unconsciousness. The third or recovery phase begins when the nausea and vomiting stop. Generally, appetite and energy return but the time required for this varies considerably. The fourth phase is the symptomless interval between episodes.

Episodes are triggered by specific events or conditions, most commonly infections such as colds and influenza, but also emotional stress, excitement, allergies eating certain foods, for example chocolate or cheese, overeating, excessively hot weather and physical exhaustion. Motion sickness and menstruation can also trigger episodes.

The severity of vomiting in CVS is a risk factor for a number of complications, the most obvious being dehydration and electrolyte imbalance, which are described in *Chapter 8*. Other complications include peptic esophagus caused by stomach acid in the vomit, **hematemesis**, which is blood in the vomit from the damaged esophagus, a Mallory-Weiss tear of the lower end of the esophagus or the stomach may bruise from violent and prolonged vomiting or retching. Finally, tooth corrosion can be DIGESTION

caused by stomach acid in a manner similar to that seen in bulimics (*Chapter 10*).

Cyclic vomiting syndrome is difficult to diagnose and many patients are initially misdiagnosed. It is usually identified from the general symptoms and medical history and by excluding more common diseases or disorders that can also cause nausea and vomiting. Diagnosis is time consuming because a repeating pattern of vomiting must be established. There is no cure for CVS. Avoiding known triggers of an episode is an obvious remedy but they cannot always be avoided. Ibuprofen taken in the prodrome phase may help prevent or alleviate an episode. Once an episode begins, treatment is supportive with bed rest and sleep in a dark, quiet room. Other medications that may be helpful are ranitidine or omeprazole which decrease the amount of acid produced. Severe nausea and vomiting may require hospitalization and intravenous fluids to prevent dehydration, since drinking water normally promotes more vomiting although it does dilute the acid in the vomit, making the episode less painful. Sedatives may help if the nausea continues. Drinking water and replacing lost electrolytes is essential in the recovery phase.

Cyclic vomiting syndrome and migraine show a number of similarities and the two may be related. Like CVS, migraine is characterized by headaches that begin and end abruptly, followed by longer periods without pain or other symptoms. They both have a number of similar triggers, including stress and excitement. Many children with CVS have a family history of migraine or suffer migraine attacks as they grow older. Given these similarities, CVS patients subject to frequent and long-lasting episodes are treated with some success using propranolol, cyproheptadine and amitriptyline that are generally used for treating migraine headaches.

Disaccharide	Structure	Products of digestion (hydrolysis)
Lactose (milk sugar)	galactose(β1–4)glucose	galactose + glucose
Isomaltose (product of starch digestion)	glucose(α 1–6)glucose	2 glucose
Maltose (product of starch digestion)	glucose(α 1–4)glucose	2 glucose
Sucrose (common sugar of plants)	glucose(α 1– β 2)fructose	fructose + glucose
Trehalose (found in fungi, some insects)	glucose(α 1–1)glucose	2 glucose

 Table 11.1 Some common disaccharides, the structure (glycosidic bond indicated in parentheses) and products of digestion



Figure 11.13 Electron micrograph of microvilli of the gastrointestinal tract. Courtesy of Emeritus Professor D.W. Fawcett.

enters the small intestine through the pancreatic duct. The salts neutralize acid from the stomach.

Proteolytic enzymes can be divided into exopeptidases and endopeptidases. The exopeptidases are aminopeptidases and carboboxypeptidases that catalytically remove amino acids from the ends of proteins and peptides (Figure 11.14 (A)). The pancreatic proteases, elastase, trypsin and chymotrypsin, are endoproteases (Figure 11.14 (B)) and hydrolyze proteins and peptides at different peptide bonds throughout the molecules to produce peptides and amino acids. The actions of endopeptidases increase the number of protein ends, effectively increasing the concentration of substrates for the exopeptidases. Pancreatic amylase continues the digestion of polysaccharides to produce disaccharides. Pancreatic lipase (Figure 11.15) hydrolyzes lipids to fatty acids and 2-monoacylglycerols but requires the presence of colipase, another protein secreted by the pancreas, for full activity. Bile released from the gall bladder enters the intestine through the bile duct and emulsifies lipids into droplets of about 1 µm diameter, which greatly increases the surface area available for lipase activity. Pancreatic esterase activity can complete the digestion to glycerol and free fatty acids (*Figure 11.16*).

The activities of many of the enzymes involved in digestion are summarized in *Table 11.3*.



Figure 11.14 The sites of digestion (hydrolysis) of proteins by (A) exopeptidase and (B) endopeptidase activities.



Figure 11.15 Model of the enzymatically active form of a pancreatic lipase molecule. PDB file 1N8S.

Zymogen	Activation mechanism	Active enzyme
Pepsinogen	HCl, pepsin	pepsin
Trypsinogen	enteropeptidase (enterokinase)	trypsin
Proelastase	trypsin	elastase
Chymotrypsinogen	trypsin	chymotrypsin
Procarboxypeptidase	trypsin	carboxypeptidase
Proaminopeptidase	trypsin	aminopeptidase

Table 11.2 Zymogens

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Location	Enzyme	Reaction(s) catalyzed
<i>Mouth</i> Salivary glands Lingual glands	α amylase lingual lipase	starch ${}^{\oslash}$ maltose triacylglycerols ${}^{\oslash}$ diacylglycerols + fatty acids
<i>Stomach</i> Chief cells	pepsin gastric lipase	proteins @ peptides triacylglycerol @ diacylglycerol + fatty acid
<i>Small intestine</i> Pancreas	amylase elastase carboxypeptidase trypsin chymotrypsin peptidase nuclease lipase esterase phospholipase	starch ⁽²⁾ maltose proteins ⁽²⁾ peptides proteins/peptides _n ⁽²⁾ proteins/peptides _{n-1} + carboxy terminal amino acid proteins ⁽²⁾ peptides proteins ⁽²⁾ peptides peptides ⁽²⁾ peptides and amino acids nucleic acids ⁽²⁾ nucleotides triacylglycerols ⁽²⁾ monoacylglycerols + fatty acids monoacylglycerols ⁽²⁾ glycerol + fatty acid phosphoacylglycerols ⁽²⁾ monoacylphospholipids + fatty acids
Intestinal mucosa and brush border	aminopeptidase dipeptidase maltase lactase trehalase sucrase-isomaltase phosphatase	proteins/peptides _n ② proteins/peptides _{n-1} + amino terminal amino acid dipeptides ② 2 amino acids maltose ③ 2 glucose lactose ③ glucose + galactose trehalose ③ 2 glucose sucrose ③ glucose + fructose maltose ③ 2 glucose nucleotides ③ nucleosides + P _j

Table 11.3 Overview of some of the digestive activities of the GIT

11.4 ABSORPTION OF THE PRODUCTS OF DIGESTION

The large surface area of the small intestine allows the rapid absorption of the products of digestion. The enzymes concerned with the final stages of digestion of a number of nutrients are located in the brush border of the enterocytes as described in *Section 11.3* or even within their cytoplasm. This ensures that the final products of digestion are produced near or within the absorptive surface of the GIT. Enterocytes are joined together by tight junctions that ensure material cannot leak from the lumen. Absorption by enterocytes is largely active and selective and they have a high metabolic rate because the transport of materials across their membranes requires considerable amounts of metabolic energy. A membrane-bound Na⁺/K⁺-ATPase uses a major proportion of this energy to catalyze the hydrolysis of ATP in the presence of Na⁺ and K⁺. The free energy from the hydrolysis is used to expel three Na⁺ from the cell and to pump two K⁺ into the cell. This may be summarized as:

 $3Na^+_{IN} + 2K^+_{OUT} + ATP + H_2O \rightarrow 3Na^+_{OUT} + 2K^+_{IN} + ADP + P_1$

Since both Na⁺ and K⁺ are being transported against their electrochemical gradients both movements are an active transport. Also, since more positive charges are being pumped out of the cell than are entering it, the effect contributes to the potential difference across the membrane, called the resting membrane potential, of about -60 mV, the inside of the cell being negative





Figure 11.16 Overview of the digestion (hydrolysis) of triacylglycerols.

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Nessar Ahmed, Maureen Dawson, Chris Smith & Ed Wood EBSCO Publishing : eBook Collection (EBSCOhost) - printed on 2/2/2019 3:48 AM via INJE UNIV LIBRARY AN: 184299 ; Ahmed, Nessar.; Biology of Disease Account: s3467669 with respect to the outside. The membrane potential of the apical membrane of the enterocyte can be harnessed to facilitate the uptake of a variety of nutrients from the lumen of the GIT. Both amino acids and monosaccharides are transported across the enterocyte luminal membrane in a Na⁺-dependent fashion. A variety of different membrane transporter proteins are responsible for the absorption of specific sugars and different groups of amino acids.

Glucose and galactose are transported across the enterocyte luminal membrane in an active, Na⁺-dependent fashion by the same transporter. One molecule of these sugars can only move through the transporter into the cell if Na⁺ ions move in at the same time (*Figure 11.17*). The concentrations of the sugars can build up within the cytoplasm, such that they are able to leave the cell through the basolateral membrane by facilitated diffusion. Other monosaccharides, for example fructose and trehalose, are absorbed only by facilitated diffusion and are absorbed to a much lesser extent.

The major initial products of protein digestion are small peptides and these are absorbed by enterocytes of the jejunum at their luminal surfaces by peptide transporter protein, called the PepT1 (*Figure 11.18*). This occurs in a H⁺-dependent fashion that resembles the uptake of glucose and galactose. Within the cytoplasm, the peptides are hydrolyzed to amino acids, ensuring a continuous sink is present to facilitate peptide uptake by the cells. The exit of the amino acids from the cells on the basolateral side also occurs down their concentration gradients. However, as peptides are moved further along the GIT, they are hydrolyzed by peptidases to free amino acids and their absorption occurs in the ileum using a number of Na⁺-dependent transporters (*Figure 11.18*), which have specificities for different amino acid side chains. Peptides



Figure 11.17 Overview of the absorption of monosaccharides by an enterocyte. Transport movements are denoted by colored lines. See text for general details.

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Figure 11.18 Overview of the absorption of amino acids and peptides by an enterocyte. Transport movements are denoted by colored lines, chemical transformations in black. See text for general details.

can also be absorbed by a paracellular route where they pass between enterocytes, rather than being absorbed across the luminal surface. Relatively large peptides can be absorbed by this method and may initiate an allergic reaction leading to food allergies (*Chapter 5* and *10*).

Digestion of RNA produces nucleotides that are further degraded to nucleosides at the brush border and which, again, are absorbed in a Na⁺-dependent manner. Catabolism within the cytoplasm converts the nucleotides to ribose phosphate and bases. Eventually the purine bases are converted to urate and the pyrimidines to uracil as shown in *Figure 11.19*.

Fatty acids, monoacylglycerols, monoacylphospholipids and cholesterol are absorbed as mixed micelles by the brush border of the enterocytes (*Figure 11.20*). The triacylglycerols and phospholipids are reformed within the enterocyte cytoplasm and packaged into large lipoprotein complexes called **chy-lomicrons** (*Chapter 14*) that are transported from the GIT in lacteals of the lymphatic system. This ensures the lipids bypass the liver and are delivered to the blood through the thoracic duct.

Water-soluble vitamins are taken up by enterocytes by a variety of mechanisms. Vitamins B_1 (thiamin) and B_2 (riboflavin) are absorbed in the upper portion of the small intestine. Thiamin is actively transferred to the portal system. Specific transporter proteins actively accumulate niacin (nicotinic acid and nicotinamide), folic acid and biotin (vitamin H) in Na⁺-dependent fashions. Pantothenic acid and the vitamers of vitamin B_6 are absorbed by diffusion. Vitamin C is absorbed in the jejunum by a Na⁺-dependent mechanism, similar to that described for glucose. The fat-soluble vitamins, A, D, E and K, are absorbed within the mixed micelles of fatty acids, monoacylglyc-



erols, monoacylphospholipids and cholesterol described above (*Figure 11.20*) and leave the enterocyte in the chylomicrons. For these reasons, a deficiency in dietary lipids means that the absorption of fat-soluble vitamins is greatly reduced.

Many minerals are absorbed in an energy dependent fashion along the length of the GIT, although Ca^{2+} and iron are mainly absorbed in the duode-

BOX 11.3 Hartnup's disease

See text for general details.

Figure 11.19 Overview of the absorption of the products of nucleic acid digestion by an

enterocyte. Transport movements are denoted by colored lines, chemical transformations in black.

Hartnup's disease, also known as Hartnup disorder, Hartnup aminoaciduria or Hartnup syndrome, was first named by Baron and coworkers in 1956 from a disorder that affected the Hartnup family of London. Hartnup disease is inherited as an autosomal recessive trait (Chapter 15), particularly where consanguinity is common. It arises from mutations to SLC6A19, a gene located on chromosome 5, whose product, a sodium-dependent neutral amino acid transporter, is expressed mainly in the GIT and kidneys. The defective gene product impairs the absorption of tryptophan and other neutral amino acids, such as valine, phenylalanine, leucine, isoleucine, across the brush border membranes of the small intestine and renal tubular epithelium. Two tissuespecific forms have been described; one affects both the GIT and kidneys, the other only the kidneys. The abnormality in amino acid transport can lead to deficiencies in neutral amino acids; the defective absorption of tryptophan may result in a niacin

deficiency (*Chapter 10*). The condition clinically resembles pellagra and may be misdiagnosed as a dietary deficiency of niacin. Tryptophan is retained within the GIT lumen and converted by bacteria to toxic indole compounds. Tubular renal transport is also defective and contributes to gross aminoaciduria. Hartnup's disease has an overall prevalence of 1 in 18000 to 42000 and, although rare, this makes it among the commonest of amino acid disorders.

Hartnup's disease usually begins at three to nine years of age but it may present as early as 10 days after birth. Most patients are asymptomatic but poor nutrition leads to more frequent and severe attacks. Patients present with pellagra-like light-sensitive rash, aminoaciduria, cerebellar ataxia, emotional instability, neurological and psychiatric symptoms that may considerably diminish their quality of life. Mental retardation and short stature have

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Figure 11.20 The absorption of the products of triacylglycerol digestion and their reformation in an enterocyte. Transport movements are denoted by colored lines, chemical transformations in black. See text for general details.

num. Dietary iron occurs in nonheme and heme forms and their absorption by duodenal enterocytes is by different mechanisms. Dietary nonheme iron occurs in ferrous (Fe(II)²⁺) and ferric (Fe(III)³⁺) forms. Ferrous iron is soluble up to a pH of about 7 but the predominant form, ferric iron, is sparingly soluble above pH 3 and is not available for absorption and must be reduced before it can be transported across the intestinal epithelium. A ferrireductase

been described in some patients. Malnutrition and a low-protein diet are the primary contributing factors to morbidity. In rare cases, severe central nervous system (CNS) damage may lead to death.

Plasma concentrations of amino acids are usually normal in Hartnup's disease. However, it may be diagnosed by demonstrating increased concentrations of neutral amino acids, such as tryptophan, glutamine, valine, phenylalanine, leucine and isoleucine in the urine, with normal levels of proline, hydroxyproline and arginine, which differentiates Hartnup's disease from other causes of gross aminoaciduria. Other tryptophan metabolites, including kynurenine and serotonin, are also found in the urine and neutral amino acids occur in the feces. Urinary indole derivatives, for example 5-hydroxyindoleacetic acid, may be demonstrated following an oral tryptophan load (*Chapter 10*). In selected patients, diagnosis may require the transport defect be identified *in vitro* using a jejunal sample obtained by biopsy.

Most patients can be treated with a high-protein diet which overcomes the deficient transport of neutral amino acids because dipeptides can be actively absorbed as shown in *Figure 11.18* and by paracellular routes. Indeed, in the developed world, cases presenting with extreme clinical symptoms are rare probably because of the protein rich diet available. Patients who are symptomatic are advised to avoid excessive exposure to sunlight and use sunscreens with a skin protection factor of at least 15. Dietary supplements of 40 to 200 mg niacin daily relieve the pellagra-like symptoms. Psychiatric treatment may help patients with severe CNS damage.

called Dcytb bound to the brush border of enterocytes reduces ferric iron to the ferrous form. Ferrous iron is then transported into the cell by a H⁺ coupled mechanism as illustrated in *Figure 11.21*. The transporter, called the divalent metal transporter 1 (DMT1), is also able to effect the absorption of a number of other divalent metal ions, such as those of cadmium, cobalt copper, lead, nickel and zinc. Heme iron is absorbed into the enterocyte by a heme receptor and, once internalized, its ferrous iron is released into the intracellular pool by heme oxygenase activity (*Figure 11.21*). Ferrous iron is exported from the enterocyte across the basal membrane by a membrane protein called ferroportin1 or Ireg1. It is then oxidized by hephaestin, a transmembrane copper dependent ferroxidase, which is necessary for effective iron transport. The ferric iron is bound by transferrin in the plasma and can be stored in erythrocytes in ferritin molecules (*Chapter 13*).

Calcium is absorbed in the upper part of the small intestine in an ionic form. This absorption requires the active metabolite of vitamin D, 1,25-dihydroxy-vitamin D_3 , and is inhibited by substances that form insoluble calcium salts, such as phosphate and oxalate. The uptake of Na⁺ has been mentioned already in relation to the active uptake of several nutrients and many anions, hydrogen carbonate, chloride and iodide, can passively follow it into enterocytes. Phosphate is actively accumulated by enterocytes.

Amino acids, monosaccharides, urate and uracil, B vitamins, vitamin C and minerals all leave the enterocytes through their basolateral membranes, enter the hepatic portal vein and are delivered to the liver. Following their absorption, many minerals are bound by intracellular proteins before being expelled through the basolateral membrane into the bloodstream where they



Figure 11.21 Uptake of iron. Transport movements are denoted by colored lines, chemical transformations in black. See text for general details.

are bound by transport proteins, such as transferrin for iron (*Figure 13.4*) and ceruloplasmin for copper. *Table 11.4* summarizes the mechanisms of absorption of the major nutrients.

Approximately 9 dm³ of fluid pass through the GIT each day. Reabsorption of water from the GIT is essential to prevent dehydration. Most, about 95%, is absorbed by the small intestine, 4% by the large intestine and only 1% is lost from the GIT.

Product of digestion	Uptake is by
Monosaccharides	Na ⁺ -dependent mechanism
Dipeptides	H ⁺ -dependent mechanism
Amino acids	Na ⁺ -dependent mechanism
Monoacylglycerols, monoacylphospholipids, free fatty acids and cholesterol	lipid soluble and absorbed across enterocyte membrane from micelles formed with bile salts
Nucleosides	Na ⁺ -dependent mechanism
Water-soluble vitamins	Na ⁺ -dependent mechanism
Fat-soluble vitamins	lipid soluble and absorbed across enterocyte membrane from micelles formed with bile salts

Table 11.4 Overview of the absorption of nutrients by the small intestine

11.5 ACTIVITIES OF THE LARGE INTESTINE

The large intestine is so named because its diameter is greater than that of the small intestine though it is, in fact, much the shorter of the two. Fluid, containing the unabsorbed products of digestion, directly enters from the small intestine at a junction that is also the site of the vestigial cecum and appendix (*Figure 11.22*). Absorption of Na⁺ and water occurs over the surface of the large intestine, which also acts as a reservoir for material resistant to digestion by GIT enzymes. However, bacterial action on this material releases some nutrients from food, for example certain vitamins as well as about 200–2000 cm³ of gas in 10–14 episodes per day. The final waste together with bacteria forms the feces, which passes to the last section of the GIT, the rectum, and is eliminated through the anus. Two sphincter muscles control elimination: the first of smooth muscle opens involuntarily in response to pressure within the rectum; the second is controlled voluntarily and allows for a conscious decision to defecate.

11.6 THE SMALL INTESTINE AND HOMEOSTASIS

Within enterocytes a portion of the monosaccharides absorbed are converted to lactate by glycolysis. Excess nonessential amino acids, especially glutamine, are used to synthesize alanine and ammonia (*Figure 11.23*). These products are then delivered to the liver in the hepatic portal vein. Converting some of the absorbed nutrients to lactate and alanine reduces the metabolic load on the liver because it can easily regenerate pyruvate from them. Pyruvate is a versa-tile liver metabolite; it is a substrate for the TCA cycle, allowing the formation of ATP during oxidative phosphorylation but it can be used for the biosynthesis of glucose and glycogen, ketone bodies, fatty acids and all but two of the nonessential fatty acids and cholesterol. The GIT is a significant contributor to nutrient homeostasis both during and after nutrient absorption because the formation of lactate and alanine continues even when absorption ceases.







Figure 11.23 The roles of the enterocyte in energy homeostasis. Transport movements are denoted by colored lines, chemical transformations in black. See text for general details.

11.7 HORMONAL CONTROL OF GIT SECRETIONS

The GIT produces a large number of hormones many of whose functions are not well understood, although some of them, together with neuronal activities, are concerned with coordinating the secretions of various digestive juices. Endocrine cells are scattered throughout the entire GIT in clusters forming a diffuse portion of the endocrine system (*Chapter 7*). Over 25 peptides have been extracted and characterized from the GIT. No deficiency states are known for any of these peptides although hormone-secreting tumors have been described.

The G cells in the antral and pyloric regions of the stomach produce gastrin. Gastrin occurs in a number of molecular forms, for example gastrin, and gastrin₂₄ are composed of 17 and 34 amino acid residues respectively. Gastrin₁₇ is the most active and has a half-life of about 8 min. Its precursor, gastring, has a half-life of approximately 40 min. The release of gastrin is stimulated by food entering the stomach from the esophagus and its function is, in turn, to stimulate release of gastric juice. Gastric inhibitory peptide (GIP) is a peptide of 43 amino acid residues secreted by the duodenum and upper jejunum. It stimulates insulin release (Chapter 7), reduces the secretions of gastrin and pepsin and inhibits gastric movements. The hormone, vasoactive intestinal peptide (VIP) is comprised of 28 amino acid residues. It is released in response to distension of the GIT by food. It stimulates the contraction of smooth muscle tissues of the GIT wall and pancreatic exocrine secretions and it also inhibits gastrin and gastric acid release. Pancreatic polypeptide is formed, as its name implies, by the pancreas and inhibits pancreatic hydrogen carbonate and protein secretions. Secretin is also produced in the duodenum and jejunum. It is a 27-amino acid residue peptide with a half-life of 17 min. Its release is triggered by acid from the stomach and it functions to stimulate the release of

pancreatic juice, the hydrogen carbonate of which helps neutralize the acid in chyme. Glucose-dependent insulinotrophic polypeptide (gastric inhibitory polypeptide) is also released in the duodenum and jejunum. It inhibits the secretion of gastric acid and stimulates insulin secretion. Mucosal cells in the upper region of the small intestine secrete cholecystokinin (CCK). Two molecular forms are produced consisting of 33 and 39 amino acid residues respectively. The release of CCK is stimulated by peptides and fatty acids in the food and, in turn, stimulates the release of pancreatic juice and contractions of the gall bladder. Motilin is a 22 amino acid residue peptide that is structurally unrelated to any other GIT hormone produced in the upper small intestine. It controls GIT movements during fasting. The ileum and colon produce peptide YY and neurotensin. The former decreases pancreatic and gastric secretions, while the latter may regulate peristalsis of the ileum. The hormone called substance P is produced along the entire GIT. Its functions include stimulating the secretion of saliva and it is also involved in the vomit reflex.

11.8 DISORDERS OF THE GIT AND ACCESSORY ORGANS

Disorders of the GIT and its accessory organs can affect the mouth, esophagus, stomach, pancreas, liver, bile duct, small and large intestines. Some of the disorders affect the exocrine pancreas, liver, stomach, small and large intestines.

DISORDERS OF THE EXOCRINE PANCREAS

Acute pancreatitis is a severe, rapid inflammation of the pancreas with varying degrees of edema (*Chapter 8*), hemorrhage (*Chapter 13*) and tissue necrosis. It arises because of an inappropriate activation of pancreatic enzymes which then autodigest pancreatic tissue. Normally, these enzymes are inactive until they reach the duodenum. The cause of acute pancreatitis is unclear, although excessive alcohol intake is believed to have a major role, but viral infections, drug reactions and pancreatic cancer have also been implicated. The clinical features of acute pancreatitis include attacks of severe abdominal pain that may extend to the back, vomiting, fever and shock. The leakage of pancreatic enzymes into the bloodstream from damaged tissue and a demonstration of increased plasma amylase activity over the first two days of an attack that returns to normal within three to five days. Treatment is symptomatic and aimed at maintaining circulation and fluid volume and decreasing pain with analgesics.

Chronic pancreatitis is a slow, progressive destruction of pancreatic tissue accompanied by inflammation and fibrosis. Like acute pancreatitis, the damage is believed to be due to autodigestion of pancreatic tissue by the activation of enzymes *in situ*. Excessive alcohol intake is the leading cause of chronic pancreatitis although many cases are idiopathic. Clinical features of chronic pancreatitis include severe and persistent abdominal pain, weight loss, malabsorption and hyperglycemia. Complications of chronic pancreatitis include diabetes mellitus (*Chapter 7*). Chronic pancreatitis is investigated using X-ray examination of the pancreas to reveal calcification that may result from the release of free fatty acids following the breakdown of fats and by examining the feces to detect steatorrhea. Treatment is directed toward management of pain and rectifying the nutritional disorders that arise from malabsorption (*see below*).

A number of tests are available to assess pancreatic function. The most widely used is the fluorescein dilaurate test which indirectly assesses the activity of pancreatic enzymes. The patient is given an oral dose of the synthetic ester, fluorescein dilaurate, that is hydrolyzed to release fluorescein by pancreatic

cholesterol esterase. Fluorescein, but not fluorescein dilaurate, is absorbed by the small intestine and transported to the liver where it is converted to fluorescein glucuronide, which is then excreted in the urine. The latter can be detected by its characteristic fluorescence. The test is controlled for variations in intestinal absorption, hepatic conjugation and renal excretion by repeating the test the next day but using an oral dose of fluorescein. The ratio of fluorescein excreted after administration of fluorescein dilaurate to that excreted after administration of free fluorescein is greater than 0.3 in normal individuals. However, a ratio less than 0.2 is indicative of abnormal pancreatic function. Ratios between 0.2 and 0.3 are inconclusive. Other investigations of pancreatic function include the para-aminobenzoic acid (PABA) test in which the patient is given 0.5 g of the synthetic peptide, benzoyltyrosylaminobenzoic acid (BTPABA). This is hydrolyzed to PABA in the small intestine by pancreatic chymotrypsin (Figure 11.24). Following its absorption, the PABA is excreted unchanged in the urine. The patient is also given a known amount of radioactively labeled PABA (14C-PABA) to correct for variations in the absorption, metabolism and excretion of PABA formed from BTPABA. The amount of PABA found in the urine is a measure of the activity of pancreatic chymotrypsin. There is reduced excretion of urinary PABA in individuals with abnormal pancreatic function.



Figure 11.24 The hydrolysis of the synthetic peptide, benzoyltyrosylaminobenzoic acid (BTPABA) by chymotrypsin activity to release para-aminobenzoic acid (PABA).

DISORDERS OF THE LIVER, GALL BLADDER AND BILE DUCT

Jaundice is the yellow discoloration of tissues due to an accumulation of bilirubin (Figure 11.5). Many disorders of the liver give rise to jaundice, although clinical jaundice may not be seen until the concentration of bilirubin in the serum is greater than 50 µmol dm⁻³. The causes of jaundice can be prehepatic, hepatic or posthepatic.

The causes of prehepatic jaundice include hemolysis, where there is an increased breakdown of hemoglobin producing large amounts of bilirubin that overloads the conjugating mechanism. Such bilirubin is mostly uncon-

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jugated and commonly occurs in newborn babies. If the concentration of serum bilirubin approaches 200 µmol dm⁻³, then phototherapy (Chapter 6 and *Margin Note 11.5*) is used to degrade it, otherwise its high concentration may cause damage to the brain called kernicterus. Other causes of prehepatic hyperbilirubinemia include hemolytic disease of the newborn due to Rhesus incompatibility (*Chapter 6*) and ineffective erythropoiesis, which occurs in pernicious anemia (Chapter 13). The commonest causes of hepatic hyperbilirubinemia are viral hepatitis and paracetamol (acetaminophen) poisoning (*Chapter 12*). There is also physiological jaundice of the newborn, a mild unconjugated hyperbilirubinemia that develops because of low activity of UDP-glucuronyltransferase, following birth. Activity increases within two weeks and the jaundice disappears. Other causes include Gilbert's and Criggler-Najjar syndromes. In Gilbert's syndrome, the affected individuals have an inherited partial deficiency of hepatic UDP-glucuronyltransferase. Patients present with a mild jaundice and occasionally suffer from abdominal discomfort but otherwise the condition is harmless. Fasting, infection, stress and excessive alcohol intake may aggravate the symptoms. Treatment of Gilbert's syndrome is by administration of phenobarbitone to stimulate glucuronyltransferase activity. Criggler-Najjar syndrome is a rare hereditary disorder characterized by a complete absence of glucuronyltransferase activity from birth. Patients suffer from severe unconjugated hyperbilirubinemia. Treatment using phototherapy in affected newborns may temporarily reduce the unconjugated hyperbilirubinemia but infants generally die within one year of birth.

One of the causes of posthepatic hyperbilirubinemia is **cholestasis** where there is failure of bile to reach the small intestine. Cholesterol is virtually insoluble in water and is maintained in an aqueous environment in vesicles combined with phospholipids and bile salts. In normal conditions, the vesicles maintain the concentration of cholesterol in bile near its saturation point. Cholesterol monohydrate crystals form when the ratio of cholesterol, phospholipids and bile salts exceeds the normal range and results in the formation of gallstones in a process termed cholelithiasis. Eighty per cent of gallstones are composed largely of cholesterol; the remaining 20% consist of calcium and bilirubin. They vary in size from that of a grain of sand to the diameter of a golf ball. In many cases, the smaller stones can be excreted in the bile duct without causing harm. Larger gallstones usually cause abdominal pain and are so large that they obstruct the flow of bile into the small intestine. However, in some cases gallstones may exist for years without causing any symptoms. When there is a complete blockage, there is little or no urobilinogen in the feces, which are pale colored due to absence of stercobilinogens. When the blockage is removed, urobilinogen becomes detectable in the urine and the feces regain their normal color. Occasionally intrahepatic obstruction arises where a blockage affects the bile canaliculi in liver cirrhosis (*Chapter 12*) or cancer (Chapter 17). This type of blockage causes an increase in the concentration of conjugated bilirubin in the serum.

It is essential to determine whether the cause of the increased amounts of conjugated bilirubin is intra- or extrahepatic because it is of diagnostic significance and determines the subsequent treatment. The degree of obstruction to the flow of bile is usually greater in extrahepatic cholestasis. Extrahepatic cholestasis may benefit from surgery to remove the gall bladder or to remove the gallstone. Nonsurgical treatments are preferred because surgery can be hazardous. Oral dissolution therapy with ursodiol and chenodiol, which are derived from bile salts, is effective in treating small, predominantly cholesterol gallstones. Treatment may be required for months to years before the gallstones are dissolved but is preferred in patients who cannot undergo surgery. In some cases, gallstones may be broken down using ultrasound waves to smaller particles that can easily be excreted.

Margin Note 11.5 Phototherapy for jaundice in newborns

(i)

Phototherapy is the most common way of treating jaundice in newborn children. It involves exposing the baby to blue light (400–500nm). This is absorbed by the bilirubin, degrading it to a form that is more water soluble and can be excreted in the feces and urine. A baby with jaundice may need repeated phototherapy over several days.

BOX 11.4 Pregnancy, cholelithiasis and cholestasis

Cholelithiasis, or the presence of gallstones, in the gall bladder (*Figure 11.25*) has a general incidence one in 1000 but pregnancy induces changes in the composition of bile that increases its frequency up to six in 100. For example, in the second trimester the bile salt pool generally decreases but biliary cholesterol levels may increase producing bile that is more prone to form stones. Additionally, emptying of the gall bladder slows in the second trimester further increasing the risk of cholelithiasis.



Figure 11.25 Gallstones in an excised gall bladder. Courtesy of Dr H.W. Ray, Southwest Tennessee Community College, USA.

The symptoms of cholelithiasis are similar in pregnant and nonpregnant patients and may present as pain in the middle of the upper abdomen, which can become more severe on eating fatty foods, jaundice and fever. Symptoms usually occur only when the stones block one of the ducts in the biliary system. Cholelithiasis is frequently asymptomatic and often the stones are only discovered by routine X-ray examination, surgery or at autopsy. An ultrasound examination of the liver is helpful in determining the presence of gallstones. Surgical treatment can be safely accomplished in the first or second trimester but should be avoided during the third trimester because of the enlargement of the uterus.

Obstetric cholestasis (OC) or cholestasis of pregnancy is a liver disorder where the flow of bile from the liver in pregnant women is reduced. It has a reported incidence of one in 10000 pregnancies in the USA. There is some evidence for a genetic link with OC. It also has an ethnic predisposition since it occurs in 0.01 to 0.02% of pregnancies in north America, but 1 to 1.5% in Sweden and 5 to 21% in Chile but is rare in black patients.

Typically OC presents in the third trimester but can occur as early as the thirteenth week. In 80% of patients it presents with severe pruritus (itching), with jaundice developing in the remaining 20% showing typical dark urine and light colored stools. In a normal pregnancy itching is not uncommon and is thought to be related to hormonal changes and stretching of the skin over the stomach as the baby grows. However, in OC the itching generally begins elsewhere, especially on arms, legs, hands and soles of the feet, face, back and breasts. It is usually worse at night, leading to sleeplessness and exhaustion, and can be of such intensity that scratching draws blood. The itching completely disappears within a week or two of the birth and does not cause long-term health problems for the mother but the condition is associated with increased health risks to the fetus. For example, studies in the USA have shown that intrahepatic OC is associated with a 12 to 44% incidence of prematurity, a 16 to 25% incidence of fetal distress and increases the perinatal mortality rate from 1.3 to 3.5%.

Acute hepatitis is caused by infection and subsequent inflammation of the liver, where liver cells are destroyed and the liver becomes necrotic. The commonest cause is viral infections, for example with hepatitis A, B, C, D and E viruses, although drugs, toxins and autoimmune reactions can also lead to acute hepatitis. The initial symptoms of acute viral hepatitis include malaise, anorexia, fever, rashes, abdominal pain, dark urine and jaundice.

Hepatitis A virus causes a mild hepatitis where patients recover usually with no complications. The virus is transmitted by contaminated food or drink, especially where sanitation is poor. Following an incubation period of 15 to 40 days, the patient develops fever, sickness and, shortly afterwards, jaundice. Hepatitis B virus is more serious with a mortality rate of 5–20% although most patients gradually recover. Hepatitis B virus spreads from one person to another via body fluids, such as blood, saliva, semen, vaginal fluids, tears, breast milk and urine. Transmission may occur during sexual activity with an infected person and vertically from an infected mother to the baby. It is commonly present in drug addicts. The symptoms develop suddenly after an incubation period of one to six months and include fever, chills, weakness and jaundice. In contrast to other types of hepatitis, more than 80% of hepatitis C virus (HCV) infections cause chronic liver disease. Approximately 170 million people worldwide may be infected with HCV. This infection is mild in the early stages and is often only diagnosed when it has already caused severe liver damage. For this reason, infection with HCV has been referred to as the 'silent epidemic'. Blood transfusions were the commonest means of

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The pathophysiology of intrahepatic cholestasis of pregnancy remains poorly understood and unfortunately no one knows why babies are at risk of being stillborn. One possibility is that the liver cannot cope with the increased amounts of hormones produced during pregnancy, which reduces the flow of bile leading to a build up of bile salts in the blood.

In addition to a complete medical history and physical examination, generalized severe itching without a rash is often the first clue to diagnosis of OC. This can be confirmed by liver function tests (LFTs) and serum bile acid tests; the latter is the most sensitive test. Normally the amounts of bile acids in blood increases before the LFTs can detect any changes. Blood tests to check blood clotting in OC are necessary prior to birth and patients may require extra vitamin K since a lack of the vitamin may decrease the effectiveness of clotting and increase blood loss during the birth (*Chapter 13*). Patients with OC require cardiotocography, that is monitoring the heartbeat of the fetus over a set period of time, ultrasound scans and blood tests. Some pregnant women may be hospitalized to evaluate the progress of the fetus. Close fetal surveillance at delivery is also desirable.

Following a diagnosis of OC, patient care involves giving general support. Specific treatments are determined by the medical history, overall health and tolerance of the patient to specific medications and by the severity of the disease. Resting as much as possible and eating a well-balanced diet that includes large amounts of vegetables, fruit and whole wheat cereals, including bread, may help, as does frequent cold baths, the use of calamine lotion and loose cotton clothing to relieve the itching. Steroids may be used to reduce the levels of bile salts in the blood and relieve the itching. For example, ursodeoxycholic acid at doses of 15 mg kg⁻¹ per day helps increase the flow of bile, reduce the level of bile acids in the blood and ameliorate the pruritus and is well tolerated by both mother and fetus. Dexamethasone, another steroid, is sometimes prescribed to increase the maturity of the fetal lungs before delivery and may also help relieve maternal itching. Parenteral vitamin K supplementation is recommended for patients with prolonged cholestasis and when blood clotting factors concentrations are abnormal.

Obstetric cholestasis may also increase the mother's risk of postpartum hemorrhage. If the well being of the mother or the fetus are judged to be at risk, then an early delivery at weeks 37 or 38 may be necessary. There does not appear to be any harmful effects to babies born to mothers with OC. Maternal symptoms usually resolve within two days of delivery and the increases in serum bilirubin and LFTs soon return to normal after delivery. Obstetric cholestasis is not thought to cause any lasting liver damage although it may leave the liver more sensitive to normal changes in the concentration of hormones leading to bouts of mild itching during the menstrual cycle just before ovulation or just prior to the start of a period. A consultant obstetrician familiar with the condition should carefully manage any subsequent pregnancies since the condition recurs in 60 to 70% of cases but it may not follow the same pattern. For example, the itching may be more severe and could begin earlier in the pregnancy.

transmission prior to the testing of blood products for HCV. Infections with hepatitis B and C viruses are associated with liver cancer (*Chapter 17*). The hepatitis D virus occurs only with or after infection with hepatitis B virus and its mode of transmission is identical to that of the B virus. Hepatitis E was initially grouped as a type C virus. It occurs in people who have been to parts of the world where this virus is endemic, such as India. It is transmitted by water contaminated with fecal material.

A clinical history of recent blood transfusions or intravenous drug use may all suggest acute hepatitis. Blood tests based on antigen–antibody reactions are conducted to establish the type of virus causing the hepatitis. Many patients present with proteinuria and bilirubinuria and show increased levels of serum alkaline phosphatase (ALP) activity. A liver biopsy will confirm the initial diagnosis. The HCV is treated with α -interferon (*Chapter 4*), otherwise patients are advised to take plenty of bed rest with adequate food and fluid intakes. A serious complication of many cases of acute hepatitis is the development of chronic hepatitis.

Chronic hepatitis is an inflammation of the liver that persists for more than six months without improvement. Its causes include autoimmune liver damage, chronic infection with hepatitis B virus and excessive drug and alcohol use. Chronic hepatitis can be divided into two histological types, namely, chronic persistent hepatitis, which has a good prognosis, and chronic active hepatitis that may respond to immunosuppressive or antiviral agents but often progresses to cirrhosis, leading to death within five years as a result of liver failure.

Cirrhosis (*Chapter 12*) is a condition where the liver responds to injury or death of some of its cells by producing strands of fibrous tissue between which are nodules of regenerating cells. Patients with cirrhosis may be asymptomatic for a long period of time before vague symptoms such as nausea, vomiting, anorexia, weakness, weight loss and edema of the legs become apparent. Its clinical complications include jaundice, **ascites**, which is an abnormal accumulation of fluid in the abdomen, GIT bleeding and hepatic encephalopathy. Cirrhosis may interfere with intrahepatic circulation causing gradual failure of liver function. Cirrhosis can be divided into three types, namely, alcoholic, postnecrotic and biliary cirrhosis. Alcoholic cirrhosis is discussed in *Chapter 12*.

Postnecrotic cirrhosis accounts for about 25% of all cases of cirrhosis and is associated with viral infections, the use of certain drugs and poisons. About 25% of postnecrotic cirrhosis cases have a prior history of viral hepatitis. Unfortunately 75% of all patients with postnecrotic cirrhosis die within one to five years. Biliary cirrhosis accounts for approximately 15% of all cases of cirrhosis and is characterized by the death of liver cells surrounding bile ducts. It is most commonly caused by an obstruction of the bile duct leading to an accumulation of bile within the liver.

Diagnosis of cirrhosis will involve palpation and X-ray of the abdomen, which often reveal an enlarged liver. A liver biopsy is required to confirm the diagnosis. Other laboratory tests may reveal anemia or hyperbilirubinemia and liver function tests (LFTs) determine increases in the activities of a number of enzymes (*see below*). There are no drugs that can arrest or reverse the fibrotic process in cirrhosis and treatment is aimed at dealing with the underlying cause, for example alcohol abuse or biliary obstruction and by treating any complications.

A number of plasma enzyme activities are used to assess liver function, including those of aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and γ -glutamyltranspeptidase (GGT). Alanine transaminase is present in both the cytosol and mitochondria of hepatocytes whereas ALT is found only in the cytosol. Liver cell damage releases these enzymes increasing their levels in the plasma. Alanine transaminase is specific for the liver whereas AST is also found in pancreatic and skeletal and cardiac muscle tissues. In hepatocellular damage, levels of AST and ALT may increase tenfold but in obstructions of the bile duct or cholestasis, the increases may be relatively slight, usually no more than two to three times their normal levels. Alanine transaminase and AST measurements are useful in monitoring the progress of hepatocellular damage where falling levels suggest an improvement in the disease. Alkaline phosphatase is found on the surface of hepatocvtes and in the microvilli of bile ducts but is not specific for liver. Its activity is increased in cholestasis. In hepatocellular disease, ALP levels may be normal or slightly raised. Falling plasma levels of ALP suggest a correction of cholestasis and may be useful for monitoring this defect. Plasma GGT levels are raised in both hepatocellular disease and cholestasis. Although the test for this enzyme is sensitive, it is not specific for liver disease as its activity is increased by some drug therapies and by alcohol. The blood protein albumin is synthesized in the liver and its concentration in plasma reflects the functional capacity of the liver. Plasma albumin concentration is low in chronic liver disease but tends to be normal in the early stages of acute hepatitis.

DISORDERS OF THE STOMACH

Gastritis is the most common disorder affecting the stomach and is characterized by inflammation and erosion of the gastric mucosa. Gastritis is idiopathic in many cases but it can be caused by irritating foods, beverages, ingested poisons, aspirin and staphylococcal exotoxin (*Chapter 2*). Gastritis may present acutely where the patient suffers from GIT bleeding, epigastric pain, that is pain on or over the stomach area, anorexia and hematemesis or vomiting of blood. Patients with chronic gastritis may have no symptoms except for epigastric pain. The possibility of exposure to irritating substances must be determined when assessing the patient's clinical history. Gastroscopy, in which a tube with a camera on its end is passed into the stomach allowing a direct visualization of its wall, can be used to confirm the diagnosis by revealing inflamed portions of the lining of the stomach. Relief from the symptoms of gastritis occurs following removal of the irritant substance or treatment of the underlying cause(s).

Atrophic gastritis is a degenerative stomach disorder characterized by chronic inflammation of the stomach with atrophy of its mucous membrane lining (*Figure 11.26*). This results in loss of gastric glandular cells and their eventual replacement by nonsecretory and fibrous tissues. Secretions of hydrochloric acid, pepsin and intrinsic factor are impaired, leading to digestive problems, vitamin B₁₂ deficiency and megaloblastic anemia. Atrophic gastritis is the result of long-term damage to the gastric mucosa and is usually detected late in life. It can be caused by persistent infection with the bacterium *Helicobacter pylori* but it can also have an autoimmune origin.

Helicobacter pylori is able to bind to the stomach lining where the bacteria release urease, which hydrolyzes urea, releasing ammonia that neutralizes the stomach acid. This allows the bacterium to penetrate into the mucosal layer. The release of bacterial and inflammatory toxic products by *Helicobacter pylori* over time results in increasing gastric mucosal atrophy. Some glandular units develop an intestinal-type epithelium; others are simply replaced by fibrous tissue. The loss of gastric mucosa decreases the amount of acid secretion that increases the gastric pH and leads to a reduced ability to kill bacteria. Ingested bacteria can survive and reside in the stomach and the upper part of the small intestine. Infection is usually acquired during childhood and, if left untreated, progresses over the lifespan of the individual in one of two main ways that have different pathological consequences. The first is a gastritis that mainly affects the antrum of the stomach (Figure 11.9). This is the most frequently observed pattern in Western countries and individuals with peptic ulcers (see *below*) usually develop this pattern of gastritis. The second pattern is a more widespread atrophic gastritis affecting, for example, the corpus, fundus and antrum with the loss of gastric glands and their partial replacement by an intestinal-type epithelium. This pattern is observed more often in developing countries and Asian individuals who develop gastric carcinoma and gastric ulcers usually present with this pattern of gastritis.

Autoimmune gastritis is associated with serum anti-intrinsic factor antibodies that reduce the amount of functioning intrinsic factor. This, in turn, decreases the availability of vitamin B_{12} and eventually leads to pernicious anemia (*Chapter 13*) in some patients. Cell-mediated immunity also contributes to the disease because T cell lymphocytes infiltrate the gastric mucosa and contribute to the epithelial cell destruction and resulting gastric atrophy.

Specific data on the incidence of atrophic gastritis are scarse. However, its prevalence mimics that of its two main causes. In both types, atrophic gastritis develops over many years and is detected later in life. *Helicobacter pylori* (*Figure 11.27*) infects approximately 20% of people younger than 40 years and 50% of those older than 60 years in the developed world. Infection is highly prevalent in Asia and in developing countries and it is estimated that 50% of the world's population is infected. Thus chronic gastritis is probably extremely common. In contrast, autoimmune gastritis is a relatively rare condition, which is most frequently observed in patients of northern European descent



Figure 11.26 Schematic showing the effects of atrophic gastritis on the stomach lining.



Figure 11.27 Schematic of the bacterium Helicobacter pylori (length 2.5–3.5 μm) based on electron micrographs of several specimens. Copyright © 2007. Taylor & Francis. All rights reserved. May not be reproduced in any form without permission from the publisher, except fair uses permitted under U.S. applicable copyright law.

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Figure 11.28 Picture of a gastric ulcer. Courtesy of Dr A.S. Mills, Virginia Commonwealth University, USA.



development of an ulcer in the stomach wall.

and in African Americans. The prevalence of pernicious anemia resulting from autoimmune gastritis is estimated to be 127 in 100000 in the UK.

Chronic gastritis frequently is asymptomatic but can present as nonspecific abdominal pain. Since gastritis often occurs in severely ill, hospitalized people, its symptoms may be eclipsed by other, more severe symptoms.

Atrophic gastritis cannot be reliably diagnosed by gastroscopy but requires a microscopic examination of biopsy specimens. *Helicobacter pylori* infections are normally diagnosed using serological tests, breath tests or antigen tests of the feces. Pernicious anemia resulting from autoimmune atrophic gastritis usually presents in patients approximately 60 years of age.

Treatment of atrophic gastritis is directed at eliminating the causative agent, to correct complications of the disease and attempt to revert the atrophic process. When *Helicobacter pylori* is the causative agent, it can be eradicated using a combination of antimicrobial agents and antisecretory agents with a success rate of about 90%. Lack of patient compliance and antimicrobial resistance are the most important factors influencing poor outcome. However, treatment of *Helicobacter pylori* infection may not lead to a reversal of existing damage unless started early but may block further progression of the disease. Some evidence suggests that β -carotene and/or vitamins C and E may reverse or reduce the risk of atrophic gastritis and/or gastritis is the development of pernicious anemia. This requires vitamin B₁₂ replacement therapy.

Ulcers are perforations of the GIT wall (*Figure 11.28*), particularly erosions of the mucosal layer related to cancer, that is, malignant ulcers, or to stomach acid, that is, peptic ulcers. Ulcers may also be named from their location, for example esophageal, gastric or stomach and duodenal ulcers. Esophageal ulcers are usually associated with hiatus hernias (*see below*) caused by acid splashing from the stomach into the lower esophagus. Gastric ulcers are relatively rare because the mucosal lining of the stomach is protected from the acid by a layer of alkaline mucus. They generally occur in patients older than 50 years of age. Duodenal ulcers are five times more common than gastric ulcers and generally occur in a younger population. More than 90% of ulcers occur in the duodenal wall, usually after it has been weakened by infection with *Helicobacter pylori*. It used to be thought that ulcers were caused by stress and excessive accumulation of HCl. However, it is now accepted that their commonest cause is infection with *Helicobacter pylori* (*Figure 11.27*) which can colonize and destroy the mucosal layer.

Peptic ulcers are linked to an increased production of acid and pepsin in gastric juice or to a reduced protection of the mucosa against gastric juice. *Figure 11.29* illustrates diagrammatically the development of a peptic ulcer. Lesions that do not extend through the mucosal lining are referred to as erosions. Acute and chronic ulcers penetrate this layer and, in serious cases, may penetrate the stomach wall. In some patients, blood vessels in the GIT wall ulcerate and lead to heavy, and in some cases fatal, bleeding. Chronic ulcers have an associated basal scarring.

Patients with peptic ulcers present with epigastric pain but their diagnosis is made on clinical grounds, supported by endoscopy, laboratory tests for assessing acid and pepsin secretion and identification of *Helicobacter pylori* infection. Treatment is aimed at eradication of the *Helicobacter pylori* infection and reducing acid output. Antibiotics (*Chapter 3*) that effectively suppress symptoms include amoxycillin, clarithromycin, metronidazole and tetracycline, and they often cure the patient. Bismuth chelate and sucralphate may also be administered to decrease the synthesis of prostaglandins that stimulate inflammation. The resulting decrease in acid production by parietal

cells and the increase in hydrogen carbonate production by mucus secreting epithelial cells have cytoprotective effects.

Zollinger-Ellison syndrome is a rare disorder that causes massive, multiple and recurrent peptic ulcers due to the excessive secretion of gastric juice from tumors affecting the pancreas or duodenum. Approximately 60% of the tumors are malignant. They are called gastrinomas because they secrete large amounts of gastrin, hence patients have an increased plasma gastrin concentration and rates of gastric acid secretion greater than 100 compared with normal rates of less than 5 mmol h^{-1} .

A diagnosis of Zollinger-Ellison syndrome usually requires demonstrating an increase in the concentration of gastrin in the patient's serum, combined with an increased release of acid in the stomach. However, in about 30% of cases the plasma gastrin concentration is normal or only slightly above normal. The pentagastrin test is used to assess the acid output of the stomach. Pentagastrin is an analog of gastrin that stimulates the release of stomach acid. Acid output is assessed before and after intramuscular injection of pentagastrin. Patients with Zollinger-Ellison syndrome have a high basal acid output and pentagastrin causes little further increase. Treatment of Zollinger-Ellison syndrome is by surgical removal of the gastrinoma.

A hernia is the protrusion of an organ or tissue out of the body cavity in which it is normally found. A hiatus hernia occurs when the upper part of the stomach is dislocated through the hole, called a hiatus, in the diaphragm, into the chest. Sliding hiatus hernias occur when the esophagus and stomach both move upwards so that the top end of the stomach protrudes through the gap in the diaphragm normally occupied by the esophagus (Figure 11.30 (A)) and these constitute 90% of cases. The remaining 10% are rolling hiatus hernias where a portion of the stomach curls upwards adjacent to the esophagus so that both it and an upper part of the stomach protrude through the gap (Figure 11.30 (B)). The causes of hiatus hernias are unknown but they may be due to intra-abdominal pressure or weakening of the gastroesophageal junction caused by trauma or loss of muscle tone. Over 50% of individuals with hiatus hernia are asymptomatic, but when symptoms do occur, they include heartburn, which is aggravated by reclining, chest pain, dysphagia, belching, pain on swallowing hot fluids and a feeling of food sticking in the esophagus. Although hiatus hernia is not usually serious, it can cause inflammation of the lower end of the esophagus leading to a back flow of gastric juices; this is called reflux esophagitis, and it may cause bleeding (perhaps anemia) or a stricture. Cancer in a hiatus hernia is very rare, but there is a slight increased risk of it developing in the inflamed area.



Figure 11.30 Schematic showing (A) sliding and (B) rolling hiatus hernias.

Data on the incidence of hiatus hernia are few but the condition increases with age and is particularly common in overweight middle-aged women and can also occur during pregnancy. The contents of the GIT are often not clearly visible by X-rays and diagnosis requires confirmation with a barium meal. This consists of barium sulfate mixed with liquid and is usually flavored. The barium in the meal lines the inside of the GIT wall and is visible because barium is opaque to X-rays making this a useful method for detecting structural abnormalities of the GIT. The presence of a hiatus hernia can also be investigated by gastroscopy.

The aim of treatment is to alleviate the symptoms. Losing weight, reducing smoking and coffee and alcohol intakes all help to relieve symptoms. The patient may be advised to avoid tight or restrictive clothing. Avoiding food intake before sleep and elevating the head of the bed help in reducing acid reflux. Medication such as antacids may be prescribed. Surgery is only used when there is strangulation of the hernia or the symptoms cannot be controlled.

DISORDERS OF THE SMALL INTESTINE

Lactose intolerance is a condition arising from an inability to express lactase. It is divided into three categories: congenital alactasia, primary acquired and secondary acquired lactose intolerance. Congenital alactasia or hypolactasia is an extremely rare condition and affected babies do not gain weight, are dehydrated and extremely unwell. Human milk is unsuitable for the baby and breastfeeding is precluded, which can also cause emotional distress in some mothers. These babies must be fed dairy-based but lactose-free or lactose-free soya formulae to survive. Primary acquired lactose intolerance usually occurs following weaning and before the age of six years and is the normal condition for approximately 70% of the world's population, the major exception being northern Europeans. It is particularly common in Asian communities and amongst blacks of African origin. Secondary acquired lactose intolerance occurs as a result of damage to the small intestinal mucosa, for example due to gastroenteritis, cows milk protein intolerance or celiac disease (*see below*).

Patients who ingest milk suffer from serious indigestion, nausea and gas, cramps, bloating and diarrhea because of the action of GIT bacteria on ingested lactose, the severity varying with the amount of lactose consumed and the tolerance level of the individual. These rather diffuse symptoms are often associated with other conditions of the GIT, such as infections with parasitic helminths (*Chapter 2*) and the protozoan *Giardia* (*Chapter 3*), inflammatory conditions, for example ulcerative colitis (*see below*), hormonal complaints, such as hypo- and hyperthyroidism (*Chapter 7*) and cancer of the colon and rectum (*Chapter 17*). Lactose intolerant patients are able to ingest a variety of milk products such as cheese, where the lactose has been removed in the whey, and yoghurt, where it has been fermented to lactate.

Lactase deficiency can be assessed by the hydrogen breath, stool acidity and lactose tolerance tests. An assay for lactase activity on a tissue sample following a biopsy of the intestinal mucosa would confirm any diagnosis. The hydrogen breath test requires the patient to drink a solution containing 50 g of lactose. If lactase is deficient, the sugar is fermented by colonic bacteria which subsequently produce dihydrogen, some of which will enter the blood and be excreted at the lung surface. Regular analyses of the breath will show the increasing amounts of hydrogen (*Figure 11.31*) in lactose intolerance. Using the appropriate sugars allows both these tests to be used in diagnosing other disaccharide intolerances, although genetic intolerances to these are rather rare. The principle of the stool acidity test is simple: undigested lactose fermented by bacteria in the colon produces lactate and fatty acids, which can then be detected in a stool sample. The lactose tolerance test is still per-



Figure 11.31 Typical results of hydrogen breath test for a control subject and a lactose intolerant patient.

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formed but only when other tests are inconclusive since it is more invasive. The patient is required to fast overnight, then drink a solution containing 50 g lactose. Several blood samples are taken over a 2-h period and their glucose concentrations determined. The amount of blood glucose indicates how well the patient is able to digest lactose. The test must be controlled by repeating the procedure using 25 g each of glucose and galactose, the constituent mono-saccharides of lactose.

The medical history, age, degree of intolerance and overall health of the patient determine treatment for lactose intolerance. In general, it can be controlled with an appropriate diet. Adding proprietary products containing lactase (*Figure 11.32*) isolated from microorganisms to dairy products prior to ingestion can also help overcome the problem.

Celiac disease is a genetically determined chronic inflammatory condition affecting the small intestine and is induced by the ingestion of wheat protein, specifically gluten, and its products. A portion of the gluten molecule forms an autoimmune complex in the GIT mucosa which stimulates T cells to aggregate and release toxins that promote lysis of enterocytes (Chapters 4 and 5). This leads to a progressive atrophy and characteristic flattening of the mucosal villi and microvilli in the upper part of the small intestine (Figure 11.33 (A) and (B)). Celiac disease is a relatively common disorder with a worldwide prevalence of 1 in 200–300. The mucosa improves morphologically when the patient is placed on a gluten-free diet but relapses occur if gluten is reintroduced in the diet. Celiac disease is accompanied by malabsorption of nutrients due to a decreased surface area over which absorption can take place. The signs and symptoms of celiac disease are surprisingly diverse and include abdominal pain, chronic diarrhea, weight loss, bone pain, fatigue and anemia. Celiac disease is diagnosed by demonstrating villous atrophy in a small intestine biopsy (Figure 11.34 (A) and (B)) and by improvements in clinical symptoms or histological tests following restriction to a gluten-free diet. Gluten-free foods are now readily available in supermarkets and health food stores. The management of celiac disease involves adherence to a gluten-free diet, which in most cases helps relieve the symptoms and allows the existing mucosal damage to heal as well as preventing further damage.

Malabsorption is a reduction in the absorption of one or more nutrients by the small intestine. It occurs as a result of a wide range of disorders that affect the GIT, pancreas, liver and gall bladder. Its causes include enzyme deficiencies, such as in lactose intolerance, chronic pancreatitis, bile salt deficiency, as in biliary obstruction or hepatitis, and intestinal diseases such as celiac disease and Crohn's disease (*see below*). The clinical features of malabsorption (*Figure 11.35*) arise because of deficiency of one or more nutrients and include anemia due to iron, folate and vitamin B_{12} deficiencies, osteomalacia due to vitamin D deficiency, edema due to hypoalbuminemia, the tendency to bleeding when vitamin K is suboptimal and generalized weight loss. Malabsorption results in retention of nutrients in the GIT lumen causing diarrhea and abdominal discomfort due to the action of GIT bacteria. Malabsorption of fats leads to their losses in amounts greater than 5 g daily and causes steatorrhea. The feces are greasy, with a pale color and have an offensive smell.

A diseased liver may be unable to synthesize bile which is required for digestion of fats and if absent can lead to malabsorption. Liver function tests can indicate the presence of liver disease and a number of blood tests are also useful in assessing liver function. These include determining the concentration of albumin in the plasma and hematological investigations such as full blood count, iron, vitamin B_{12} and folate and can indicate the type of malabsorption. Investigations of malabsorption also include microbiological examination of feces to identify any pathogens present. The pentose sugar xylose is absorbed in the small intestine but is not metabolized and is excreted unchanged in



Figure 11.32 A proprietary product containing lactase used for the digestion of lactose prior to ingestion.



Figure 11.33 Photomicrographs of (A) healthy villi (V) and associated crypts of Lieberkuhn (C) and (B) the mucosal lining from a celiac patient. Note the degeneration of the villi.





Figure 11.34 Photographs of gastrointestinal tract biopsies from (A) a healthy person and (B) a celiac patient. Note the degeneration of the villi.



Figure 11.35 Schematic showing the clinical features associated with malabsorption.

the urine. This property is exploited in the xylose absorption test to assess the malabsorption of carbohydrates. The patient fasts overnight, empties the bladder and drinks a 500 cm³ solution containing 5 g xylose. In normal individuals, the serum xylose concentration increases above 1.3 mmol dm⁻³ one hour after the test. After 5 h, the concentration of xylose in the urine increases to more than 7.0 mmol dm⁻³. Significantly lower concentrations of xylose occur in the serum of patients with carbohydrate malabsorption. However, care must be exercised since some bacteria colonizing the small intestine are capable of metabolizing xylose and a number of renal diseases can also lead to reduced concentrations.

Malabsorption of fat can occur in a number of pancreatic and intestinal disorders. Bacteria colonizing the small intestine may break down bile acids, reducing their effective concentration and causing malabsorption. A fecal fat test can assess fat malabsorption. The test involves collecting feces over a period of three days after which their fat content is assessed chemically. Normally, up to 5 g of fat is lost in the feces each day but more is lost during malabsorption giving rise to steatorrhea.

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BOX 11.5 Food allergies

A food allergy is a reaction of the immune system to food components that are allergens (Chapter 5). Foods commonly associated with allergies include milk, eggs, peanuts, tree nuts, soy, wheat, fish and shellfish, which are protein rich, and account for over 90% of all food allergies. The antibodies responsible for food allergies are IgE molecules that react with allergens to trigger the release of histamine (Figure 11.36). Histamine is largely responsible for the symptoms but these differ between patients and can differ in the same individual when exposed to different allergens. Symptoms include skin irritations, for example rashes and eczema, itchy nose and eyes, sneezing, excessive nasal mucus, coughing and shortness of breath, nausea, vomiting and diarrhea. Skin rashes, such as nettle rash (also called urticaria or hives), can appear but tend to last only a few days. Occasionally, patients present with long-lasting, chronic skin reactions such as scaly patches. Food allergies are relatively common and affect 1-2% of adults and up to 8% of children in the UK. Some individuals may experience the severe reaction called anaphylaxis described in *Chapter 5*. This is triggered by a small amount of food and is a rare but potentially fatal condition in which several different parts of the body experience allergic reactions including skin rashes, swollen throat and difficulties in breathing, nausea, vomiting, diarrhea, hypotension and unconsciousness. Symptoms usually appear within minutes of exposure to the allergen and can last several hours. An unusual form of anaphylaxis occurs following the consumption of allergens within a few hours of exercising and is referred to as exerciseinduced anaphylaxis.

Food intolerance refers to the less well-defined condition occurring in some people when they eat certain foods and is characterized by headaches, muscle and joint aches and pains, and tiredness. The less well-defined symptoms make the condition harder to diagnose compared with classical food allergy. Examples of food intolerance include celiac disease and lactose intolerance.

The diagnosis of food allergy involves taking a clinical history from the patient, focusing on past allergic reactions and considering seasonal or environmental cues. This is followed by a clinical examination to detect characteristic signs and symptoms affecting the eyes, skin and nose. Skin prick testing is often performed. The procedure introduces a small amount of allergen into the skin and is generally safe. A tiny puncture is made with a lancet through a drop of allergen placed on the skin usually of the forearm. A positive reaction to the allergen usually means the patient is allergic and is indicated by itching within a few minutes; the affected site becoming red, swollen and having a raised weal in its center. The weal enlarges to a maximum size within 15 to 20 min and is measured and recorded. A negative



Figure 11.36 Schematic showing the release of inflammatory mediators in response to a food allergy. See text and *Chapter 5* for details.

response indicates that the patient is insensitive to the allergen under test. Blood tests, such as the radioallergosorbent (RAST) test, to detect the presence of IgE antibodies may be used but can only indicate an allergy if the specific IgE is present in the blood. However, there is no clear relationship between the level of blood IgE and the severity of the allergy. Occasionally, a challenge test may be performed where the suspected food is given to the patient first by touch and then by ingestion in increasing amounts and the response monitored. Challenge tests should always be performed under supervised conditions in a hospital or clinical setting, so that any clinically serious reactions can be detected and managed.

Food allergy is usually treated by avoiding the offending food. In some cases, complete elimination of the food for one to two years results in a loss of clinical symptoms although certain allergies, for example those associated with the intake of fish or peanuts, may persist for life. It is vital that consumers are provided with clear information on the composition of foods they purchase. Food avoidance may have serious nutritional consequences, particularly when a key nutrient is removed from the diet. Immediate medical attention is necessary when anaphylaxis occurs and usually involves an injection of adrenaline to dilate airways and blood vessels by relaxing smooth muscle tissues.

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BOX 11.6 Diarrhea

Diarrhea is the frequent passage of feces that are larger in volume and more fluid than normal. It is not a disease but a symptom of some other underlying conditions that result in abrupt increases in intestinal movements. The accelerated movement of the contents through the GIT leaves insufficient time for fluid reabsorption and produces watery stools. A two-way flow of water and electrolytes occurs between the GIT lumen and the basolateral extracellular fluid (ECF). Water enters the GIT in food and drinks and in various secretions. In the small intestine, the secretion of water and electrolytes normally occurs in the crypts of Lieberkuhn. Sodium chloride is transported from ECF into epithelial cells across their basolateral membranes. Secretory stimuli increase the permeability of luminal membranes of the crypt cells allowing chloride ions to move into the GIT lumen. Sodium ions, however, are returned to the ECF by the action of the Na⁺/K⁺-ATPase of the basolateral membranes. The movements of these ions generate an osmotic gradient and water flows passively from the ECF into the lumen through intercellular channels. Water reabsorption is also driven by osmotic gradients, which are formed when solutes, particularly sodium ions, actively enter enterocytes. Absorption of sodium ions may occur by direct transport as the ion, or be exchanged for hydrogen ions or linked to the absorption of glucose, amino acids or chloride ions.

Following absorption, sodium is transported out of enterocytes across the basolateral membrane into the ECF by the Na⁺/K⁺-ATPase. This increases the osmolality of the ECF and water moves passively into it from the GIT lumen. These processes maintain an osmotic balance between GIT contents and ECF in the intestinal tissue. However, since fluid absorption normally exceeds secretion, the net result is fluid absorption. More than 90% of the fluid entering the small intestine is absorbed, with only about one dm³ of it reaching the large intestine. Here further absorption occurs and only 100 to 200 cm³ of water is lost in the feces daily.

Diarrhea arises when water and electrolyte transport becomes disordered, for example by increased secretion, decreased absorption or both, and an increased volume of fluid enters the large intestine. When this exceeds the absorptive capacity of the large intestine it results in diarrhea.

Diarrhea may result from one of two principal mechanisms, secretion and osmotic imbalance. These mechanisms are not exclusive; intestinal infections can cause both types and, indeed, both may occur in a single individual. Secretory diarrhea is the more common of the two and is caused by an abnormal secretion of water and salts into the small intestine. This occurs when the reabsorption of sodium ions is impaired but the secretion of chloride ions in the crypts of Lieberkuhn is maintained or increased. This produces a net secretion of fluid resulting in the loss of water and salts from the body in watery stools; this causes dehydration. Infectious diarrhea may result from the actions of bacterial toxins or viruses on the GIT mucosa (*Chapter 2*). Osmotic diarrhea results when a poorly absorbed, osmotically active substance is ingested, causing water and salts to move rapidly across the GIT lining to maintain the osmotic balance. The effects depend upon the osmolarity of the solution. If the substance is taken as an iso-osmotic solution, water and solute will pass through the GIT, with no net absorption causing diarrhea. If taken as a hyperosmotic solution, water and some electrolytes will move from the ECF into the GIT lumen increasing the volume of the feces and causing dehydration. Furthermore, because the loss of body water is proportionally greater than the loss of sodium and chloride ions, hypernatremia also develops (*Chapter 8*).

Diarrhea results in losses of large amounts of sodium, chloride, potassium and hydrogen carbonate ions. Acute effects result from the loss of water and electrolytes, leading to dehydration, metabolic acidosis, because of the loss of hydrogen carbonate and potassium depletion (*Figure 11.37*). The dehydration is the most dangerous in the short term because a decreased blood volume (**hypovolemia**) can result in cardiovascular collapse and death if not treated promptly (*Chapter 8*). The aim of managing diarrhea is to correct dehydration and electrolyte deficits. Fluids can be replaced either orally or intravenously.





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Crohn's disease is a chronic inflammation, usually of the ileum, although it can affect any part of the GIT. The inflammation tends to be patchy but extends throughout the layers of the intestinal wall thickening the wall and narrowing the lumen. The cause of Crohn's disease is unclear although viruses and bacteria have been implicated. Patients with Crohn's disease suffer from lack of appetite, abdominal pain, diarrhea and weight loss. A biopsy of the GIT is used to detect the characteristic changes associated with Crohn's disease. Treatment involves using anti-inflammatory drugs, such as 5-aminosalicylic acid, although surgery may be required in severe cases.

DISORDERS OF THE LARGE INTESTINE

Ulcerative colitis is characterized by chronic inflammation and ulceration of the colon that is distinctive, in that it affects only its mucosal lining. The lining is also affected by numerous hemorrhagic ulcerations. The cause of ulcerative colitis is not entirely clear but is believed to be autoimmune in origin (Chapter 5). Patients with ulcerative colitis suffer from abdominal pain, fever, weight loss and bloody diarrhea. Diagnosis of ulcerative colitis is made following colonoscopy where a biopsy from the colon is taken to detect the characteristic histological changes. Ulcerative colitis is treated with anti-inflammatory drugs, such as 5-aminosalicylic acid, although surgical removal of the affected region may be necessary in severe cases.

CASE STUDY 11.1

Alice, a five-year-old child, presented with loss of weight, abdominal distension and obvious signs of anemia. Her stools were loose, bulky, pale colored and had an offensive smell. A variety of clinical tests were ordered with the following results (reference ranges are shown in parentheses):

29 g dm⁻³ (32-48 g dm⁻³)

4 µmol dm⁻³ (10–30 µmol dm⁻³)

Xylose absorption 0.5 g in 5 h (>1.2 g in 5 h) Fecal fat 29 g / 3 days (<15 g/3 days) Jejunal biopsy showed villous atrophy.

Questions

- What is the most likely diagnosis? (a)
- How should Alice be treated? (b)

CASE STUDY 11.2

Serum albumin

Serum iron

It was noticed that Sadaf, a fine art student recovering from an attack of influenza, was slightly jaundiced. Worried that she may have hepatitis, her doctor asked her to provide some blood and urine for laboratory investigation. Test results are shown below (reference ranges are shown in parentheses):

Hemoglobin	140 g dm ⁻³ (115–155 g dm ⁻³)
Reticulocyte count	1.5 % (1–2%)
Urine bilirubin	Negative (Negative)

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What is the most probable diagnosis to account for these signs and symptoms?

Serum	bilirubin	60 μmol dm ⁻³ (3–20 μmol dm ⁻³)
Serum	ALP	74 IU dm ⁻³ (30–90 IU dm ⁻³)
Serum	AST	35 IU dm ⁻³ (10–50 IU dm ⁻³)

CASE STUDY 11.3

Serum Na⁺

Mark, a 52-year-old plumber, was admitted to hospital because of severe abdominal pain. The pain had started suddenly about 15 h previously. On questioning, Mark admitted to being a heavy alcohol drinker over many years. Clinical examination showed that Mark had a tender abdomen and was in mild shock. Radiographic examination did not show any evidence of intestinal obstruction. Biochemical tests gave the following results (reference ranges are shown in parentheses):

Questions

- (a) What is the most likely diagnosis?
- (b) Why does Mark have a high serum urea concentration?

 K^+ 4.2 mmol dm⁻³ (3.6–5.0 mmol dm⁻³)

140 mmol dm⁻³ (135–145 mmol dm⁻³)

11.9 SUMMARY

The GIT and its associated organs are necessary for the digestion of food and the absorption of nutrients derived from food. Digestion takes place in the mouth, esophagus, stomach and small intestine, with the bulk of ingested water being absorbed in the latter. The pancreas provides enzymes for digestion in the small intestine while the liver secretes bile, containing detergents that aid in the digestion of fats. Most nutrients from digestion are carried to the liver in the hepatic portal vein.

The GIT also contributes to nutrient homeostasis, through metabolic reactions that take place in GIT enterocytes, delivering metabolic products such as lactate to the liver. The GIT also produces a number of hormones that help in coordinating its activities.

Disorders of the pancreas, such as acute and chronic pancreatitis, are serious conditions that may be fatal. Disorders of the liver may be caused by drugs, poisons, viruses, and alcohol or by blockage of the bile duct, as in cholestasis. Liver disorders may be diagnosed by assaying several enzymes, together with an X-ray examination and palpation to detect a swollen liver. Jaundice is a frequent complication of liver disease. Disorders of the GIT include gastritis and ulcers that are associated with infection of *Helicobacter pylori*, intolerance to certain nutrients, such as lactose, celiac disease and malabsorption.

Questions

- 1. Which of the following is associated with the development of peptic ulcers?
 - a) smoking;
 - b) Helicobacter pylori;
 - c) weight loss;
 - d) celiac disease;
 - e) lactose intolerance.
- 2. Which one of the following tests is best used to assess pancreatic function?
 - a) fecal fat test;
 - b) serum bilirubin;

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- c) oral glucose tolerance test;
- d) fluorescein dilaurate test;
- e) xylose absorption test.
- 3. Qiuyu, a 32-year-old from China, entered England to study as a mature research student. Wishing to 'integrate' fully in her new environment she adopted many of the dietary habits typical of the country. After six healthy months, she unfortunately suffered a bout of viral gastroenteritis that required hospitalization. Qiuyu, fortunately made a complete recovery and was able to continue her new lifestyle. However, she again became ill again, but with severe indigestion, abdominal cramps, intestinal bloating and periods of diarrhea. Symptoms were most pronounced about one hour after breakfast.
 - a) Suggest the most probable cause of Qiuyu's symptoms.
 - b) What test(s) could be used to help your initial diagnosis? Include any precautions that may be necessary in your clinical investigations?
 - c) Assuming your initial diagnosis is correct, what treatment do you recommend for Qiuyu?
- 4. List some possible causes of jaundice.
- 5 List four causes of malabsorption.

FURTHER READING

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