14. Digestive System

14.1 Introduction

All the water, nutrients, vitamins, minerals and electrolytes required for growth and maintenance are absorbed from the digestive tract and transported to other tissues by the blood stream. However, only a small portion of the ingested solid material - small lipid- and water-soluble molecules - may be absorbed unchanged. The complex macromolecules that form the bulk of the diet must first be reduced to simpler, metabolizable forms by *digestion.* This is accomplished in the lumen of the digestive tract by exposing the ingested material to specific sequences of mechanical and chemical events.

The *digestive tract* is a tube extending from the mouth to the anus and includes the pharynx, oesophagus, stomach, small intestine and large intestine. Food entering the tract is mixed and propelled along the tract as a result of skeletal and smooth muscle activity. As ingested material progresses through the tract the complex molecular structures may be broken down by hydrolytic enzymes that act in either acidic or neutral environments. The digestive juices are secreted from glandular tissue that forms part of the intestinal wall or from glands that lie outside the intestinal tract (the salivary glands, pancreas and liver). The secretions of the latter enter the digestive tract through ducts.

The *digestive process* starts in the mouth where the food may be ground and mixed with saliva. Here the addition of a salivary amylase to the food begins the breakdown of starches. After passage through the pharynx and oesophagus this material enters the stomach where it is acted on by acid and gastric proteases. However digestion in the stomach is limited and one of the main functions of the stomach is to act as a store and hopper that slowly releases partially digested material (chyme) into the small intestine. The final phases of digestion occur in the small intestine and colon. In the small intestine the chyme is broken down by the actions of bile, pancreatic enzymes (i.e., protease, lipase and amylase) and enzymes released from desquamated epithelial cells. Most of the products of digestion are absorbed by the small intestine - some by specific transport mechanisms - and the residue passes into the large intestine. There is little digestion in the colon but salt, water and some vitamins (produced by bacteria) are absorbed.

Structure of the Digestive Tract

From the mouth to the anus the digestive canal is lined by a mucous membrane (*mucosa*. In the mouth, oesophagus and anus, where there can be considerable abrasion, the epithelial layer is of a stratified squamous variety some ten to fifteen cells thick. In regions devoted to absorption and secretion a single-layered columnar epithelium is found. Absorption is enhanced in these regions by folding and by the formation of villi, which are finger-like projections of the mucosa.

The *muscles* surrounding the digestive tract may be striated or smooth muscles. The striated muscles are found in the upper region of the tract (the mouth, pharynx and oesophagus) and at the anus. In between these regions the tract is surrounded by an external layer of smooth muscle, the *muscularis externa*, composed of an outer layer with its fibres

oriented in a longitudinal direction and an inner layer containing fibres with a circular orientation. This part of the tract contains a thinner, smooth muscle layer, the *muscularis mucosae*, at the base of the mucous membrane. The thicker outer coat is involved in the propulsion and mixing of food, while the muscularis mucosae may control the folding and shape of the mucosa.

The blood vessels, lymphatics and *nerves* to the intestinal tract travel in the mesenteries.

Intrinsic nerves in the tract between the lower oesophagus and the rectum come from the *myenteric (Auerbach's) plexus* which lies between the outer longitudinal and circular muscle layer, and from the *submucosal (Meissner's) plexus* which lies between the circular muscles and the muscularis mucosae. These intrinsic networks are composed of excitatory and inhibitory motor nerves to the smooth muscle fibres and excitatory innervation to secretory cells and hormone-releasing cells. The input to these plexuses comes from the autonomic nervous system and from intrinsic chemo- and mechanoreceptors which may have their sensory terminals in the epithelial sheet.

Regulation of the Digestive System

The motor and secretory activity of the GIT is regulated and coordinated by nerves and hormones. Nervous control can be subdivided into intrinsic and extrinsic components. *Intrinsic nervous control* involves local reflexes confined to the wall of the gut itself and effective over rather short distances (cm) along the tract. Receptors responsive to a variety of stimuli (i.e., stretch, pH, osmolality, products of digestion) activate afferent fibres whose cell bodies are located in the intramural plexuses. These neurones synapse within the plexuses with efferent neurones supplying smooth muscle, secretory cells or hormone-producing cells in the locality.

Extrinsic nervous control is mediated via receptors and afferent fibres, the cell bodies of which are found within the intestinal plexuses or the dorsal roots. Some of the information conveyed may reach areas within the brain, and the efferent outflow conveyed by *sympathetic* or *parasympathetic* nerves from the CNS may reach synapses within the intramural plexuses or secretory organs (salivary glands, liver, pancreas) directly. These extrinsic pathways and reflexes through prevertebral ganglia allow regulation and coordination of GIT activity over greater distances.

A variety of hormone-secreting cells of neuroectodermal origin are located within the epithelial cell layer and are bathed directly by the luminal contents. Hormonal release may be a consequence of nerve stimulation or of changes in luminal composition (i.e., pH, osmolality, products of digestion). These hormones (i.e., gastrin, secretin, cholecystokinin) diffuse into the wall of the gut and may act locally to alter gut activity. Their local actions are called *paracrine effects.* In addition, they may enter the capillaries and be transported through the circulation to exert their effects on more distant parts of the alimentary system or on other organs.

Nervous control in the GIT is found exclusively in the upper part (mouth, oesophagus) and at its termination (anus) where rapid but short-lasting responses are required. Nervous and hormonal control play equally important roles in the control and regulation of gastric activity. In the intestine, motility is more dependent on neural mechanisms but in the regulation of secretions of liver and pancreas, hormonal control is the more important.

14.2 Motility of the Digestive Tract

Both longitudinal movement and mixing of the luminal contents are essential if efficient digestion and absorption are to be maintained. In the upper regions of the digestive tract, where the movement of food is rapid, motility is controlled directly by the CNS. Where the movement is concerned mainly with mixing and slow propulsion (during digestion and absorption), the motility is regulated by mechanisms inherent in the muscle (*myogenic mechanisms*), *by neural mechanisms* and by *hormones.*

The motility of the lower tract is largely under the influence of the myenteric plexus which in turn is influenced by the extrinsic nerves (parasympathetic and sympathetic) and the submucosal plexus. *Most parasympathetic fibres are excitatory and the sympathetic fibres are inhibitory.* The inhibitory influence of the sympathetic nerves, which largely terminate in the myenteric plexus (or on blood vessels), is due predominantly to their inhibitory effect in the plexus. These nerves were once believed to be the only fibres involved in the inhibitory control of motility but more recently stimulation of preganglionic 'parasympathetic' fibres (and stretch receptors from the epithelium) has been found to have an inhibitory effect on smooth muscle. This effect is mediated by postganglionic *non-adrenergic inhibitory fibres* which release an unidentified transmitter, possibly ATP or vasoactive intestinal peptide.

Mouth and Oesophagus

Chewing

When the food enters the mouth chewing movements (mastication) reduce the size of the particles and mix them with saliva; both of these actions contribute to the taste, odour and swallowing of food. In man the mechanical effects are accomplished by the cutting action of the incisor teeth and the crushing movements of the molar teeth.

The chewing movements are under voluntary control and involve the coordinated action of the lower mandible, cheeks and tongue. The lower jaw is usually held closed as a result of reflex (muscle spindle) activity but a conscious decision or the presence of food in the mouth may momentarily inhibit this reflex and initiate jaw opening. The alternate activation and inhibition of the nerves to the opening and closing muscles results in chewing. The appropriate rhythm, force and degree of occlusion are provided reflexly and as the reflex is unilateral the chewing force is exerted largely on the side containing the bolus of food.

Swallowing

Swallowing involves the movement of food from the mouth to the oesophagus, movement down the oesophagus and movement from the oesophagus to the stomach. Initially the tongue forces a bolus of food to the rear of the mouth. The stimulation of receptors in the

posterior wall and soft palate then results in the activation of the *swallowing reflex.* This activity is coordinated within a medullary *swallowing centre* and the reflex once initiated cannot be stopped. It involves the elevation of the *soft palate* to close the nasopharynx, the raising of the *larynx* and approximation of the vocal cords to close the *glottis,* the inhibition of breathing, and the relaxation of the *upper oesophageal sphincter.* Lesions in the region of the swallowing centre in the medulla interfere with this coordinating activity and may be fatal. Once the cam-like action of the tongue has passed the food into the pharynx, the pharyngeal skeletal muscles contract and propel the bolus of food into the oesophagus. The pressure generated, which can be up to 100 mmHg above atmospheric, normally provides the major force propelling the food along the oesophagus.

In the oesophagus a *peristaltic wave* (a ring of contraction preceded by a region of relaxation) propels viscous material toward the stomach. Fluid material travelling under the influence of the pressure generated by swallowing and by gravity may arrive at the stomach before the contractile wave. The peristaltic wave travels at approximately 5 cm/sec and takes approximately 8 sec to travel the length of the oesophagus. The pressures generated by peristalsis in the oesophagus range from 30 to 120 mmHg.

The movement of the food bolus from the oesophagus to the stomach is accomplished after relaxation of the *lower oesophageal sphincter.* This sphincter is the terminal 4 cm of the oesophagus and is anatomically not much different from adjacent areas. It is normally closed (resting pressure 10-15 mmHg) to prevent reflux of the stomach contents which would otherwise occur because the pressure in the stomach (5-10 mmHg) is higher than that in the thoracic oesophagus (-5 mmHg). If the acid contents of the stomach enter the oesophagus the sensation of 'heartburn' may be experienced.

The sphincter relaxes some 1 to 2 sec after swallowing is initiated, remains relaxed for 8 to 9 sec and then contracts. Between swallowing movements the tone of this sphincter is maintained by slight contraction of the smooth muscle layer. As some tone is maintained in the denervated tissue, intrinsic activity appears to be involved in maintaining this contraction.

The *primary peristaltic wave,* which is initiated by swallowing, normally clears the oesophagus of food but if particles remain in the oesophagus *secondary peristaltic waves* may begin. These waves arise as a result of distension or irritation of the oesophagus and involve the swallowing centre. The secondary waves, which arise without any awareness, commence at the upper oesophageal sphincter and progress to the stomach.

Stomach

The stomach receives, stores and partially digests food prior to its gradual release into the small intestine. The stomach has three outer smooth muscle layers (the longitudinal, circular and oblique layers) which have both mixing and propulsive roles.

Gastric Motility

Between meals the stomach contains a small volume (about 50 mL) and the smooth muscle contracts only occasionally. As food enters the stomach the intragastric pressure may rise but the increase is only slight due to the elasticity of the stomach wall and to the relaxation of the smooth muscle cells. This *receptive relaxation* of the smooth muscle results from stimulation of stretch receptors in the oesophagus and proximal stomach and results in activation of postganglionic non-adrenergic inhibitory neurones which arise in the myenteric plexus.

For the first hour after ingestion of a meal shallow waves of contraction move over the stomach. These gradually deepen until ring-like peristaltic contractions, starting high on the stomach in the fundus, sweep over the body and antrum toward the pylorus. However little pressure is generated within the body of the stomach. As the contraction pass over the antrum and pylorus they progress more rapidly and become more forceful. During these contractions the pressure in the antrum may rise to 15-25 mmHg and a small quantity of the gastric contents now referred to as *chyme* enters the small intestine through the *pyloric canal* or sphincter. However the canal, which is normally relaxed, closes rapidly during each contraction and most of the antral contents are squirted back into the body of the stomach. This is termed *retropulsion* and has a strong mixing action that helps to break down the food.

Control of Gastric Motility

The contractile activity of the stomach is regulated by *myogenic, neural* and *hormonal* mechanisms.

The frequency of the contractions (about three per minute) and their coordination depend on the spread of *'slow waves'* of depolarization (10-25 mV) throughout the smooth muscle layers. This rhythmic depolarization (basic electrical rhythm) is myogenic in origin. Slow waves occur most frequently in the fundic portion of the longitudinal smooth muscle and can be initiated in neighbouring regions by passive current spread through gap junctions. Thus the slow waves are conducted around and along the stomach wall. If the slow waves exceed threshold, spike-like potentials are initiated and a contraction follows. Thus it is the slow waves during normal digestion that determine the *frequency* and *conduction velocity* of the peristaltic contractions. The ionic basis of the slow waves is not understood but it has been attributed to an electrogenic pump and to permeability changes in the plasma membranes of the smooth muscle.

The force of gastric contractions is regulated by neural and hormonal mechanisms. Vagal stimulation of cholinergic motor nerves or gastrin released from the antral mucosa lowers the membrane potential of the smooth muscle cells. Subsequent slow waves then lower the membrane potential further and for a longer time. The resulting potentials in the smooth muscle cells then induce a more powerful contraction. In contrast to this the non-adrenergic inhibitory nerve fibres cause hyperpolarization, and thus inhibit gastric motility.

Gastric emptying. The rate at which the stomach empties is determined by its motility. The factors that regulate gastric emptying are the same as those that regulate gastric secretion

- they are increased or decreased together. Essentially both are influenced by the physical and chemical nature of the gastric and duodenal contents.

Vomiting

Vomiting results in the rapid expulsion of the stomach contents through the mouth. It involves (i) forceful inspiratory movements when the glottis and nasopharynx are closed, (ii) relaxation of the oesophagus, lower oesophageal sphincter and body of the stomach, (iii) contraction of the pyloric region of the stomach and possibly the duodenum forcing duodenal contents into the body of the stomach, and (iv) contraction of the abdominal and thoracic muscles. When the descent of the diaphragm coincides with contraction of the abdominal muscles, the elevation of abdominal pressure forces the gastric contents out through the mouth.

Integration of the vomiting sequence occurs in a medullary *vomiting centre* that is anatomically and functionally associated with the centres governing respiration. It is influenced by the adjacent 'chemoreceptor trigger zone' in the area postrema which may be stimulated by a variety of drugs (i.e., morphine and its derivatives) that induce vomiting.

Small Intestine

Most of the digestion and absorption of food takes place in the duodenum and jejunum. Thus the motility of this section serves to mix the chyme from the stomach with the digestive juices secreted by the pancreas and liver and also to expose the luminal contents to the intestinal wall across which absorption occurs. In addition, the intestinal contents are slowly propelled toward the large intestine.

Motility of the Small Intestine

The above functions are accomplished by two motility patterns, namely, segmentation and peristalsis.

1. *Segmentation* is the alternate contraction and relaxation of complete segments of the small intestine. As the chyme from one contracting segment is forced into adjacent relaxed areas, this motility pattern thoroughly mixes the luminal contents. The electrical basis of this contractile pattern appears to be slow waves. The factors that result in segmentation rather than peristalsis are not understood but, since the contractile band does not progress, this pattern has little propulsive action. The length of each segment involved in these contractions ranges from 8 to 10 cm in the duodenum to 0.5 to 1 cm in the ileum. Likewise the frequency of the segmental contractions decreases down the length of the human small intestine from about 12 contractions per min to 9 contractions per min.

2. Short *peristaltic contractions* travelling 10-15 cm are the main propulsive force in the small intestine. These moving, ring-like contractions are preceded by a more distal region of relaxation as they move towards the colon. They can be elicited by luminal distension. More protracted peristaltic contractions (rushes) that traverse the length of the small intestine are abnormal.

In fasting man the antrum and small intestine appear to undergo a characteristic pattern of contractility consequent upon electrical activity called the *interdigestive myoelectric complexes.* These complex electrical events indicate that a pattern of motility - a quiescent period, a period of segmentation and then a period of peristalsis - travels down the small intestine. In the dog this complex lasts about 40-80 min at any one point and traverses the small intestine in about 200 min. When one complex reaches the terminal ileum another starts in the antrum. These patterns of motility effectively 'clean out' the stomach and small intestine.

Control of Small Intestinal Motility

The motility of the small intestine depends on *myogenic, neural* and *hormonal* mechanisms.

As in the stomach the rhythmic contractile activity of the small intestine results from regular slow waves of depolarization of the smooth muscle cells. Similarly, contraction in a segment of the small intestine is coordinated by the spread of slow wave activity from cell to cell with consequent initiation of action potentials. However, as already mentioned, in contrast to the stomach the small intestine exhibits a decrease in the frequency of contractions along its length. This decrease is the result of successive portions of the intestine having a lower intrinsic frequency of slow waves, the frequency of slow waves being highest in the duodenum. However, more distal portions are unable to follow this high frequency; they occasionally 'miss' a slow wave and the frequency decreases.

Stimulation of the postganglionic cholinergic enteric nerves increases the amplitude of contractions while stimulation of the sympathetic or non-adrenergic inhibitory nerves inhibits contractions. Since the motility of the small intestine continues in the absence of extrinsic nerve supply, it has been argued that the neural regulation of motility is mainly intrinsic. This argument is supported by the observation that isolated segments of the small intestine increase their contractile activity in response to distension, acids, the products of digestion and placing hypertonic solutions in the lumen.

The extrinsic nerves, however, also play a role and their importance is indicated by the presence of the following reflexes:

(i) The *intestino-intestinal inhibitory reflex* in which distension of one intestinal segment causes complete intestinal inhibition;

(ii) the *ano-intestinal inhibitory reflex* in which distension of the anus causes intestinal inhibition; and

(iii) the *gastro-intestinal reflex* in which food entering the stomach causes excitation of intestinal motility.

The role of hormones in the control of intestinal motility is less clear but *cholecystokinin (CCK)* stimulates motility.

For chyme to enter the large intestine it must pass through the *ileocaecal sphincter* which in man is approximately 4 cm long. This sphincter at rest is closed by a pressure of some 20 mmHg. During normal movements this pressure is reduced in association with peristaltic contractions in the terminal ileum and the chyme moves into the large intestine.

Large Intestine and Rectum

The progression of chyme through the large intestine is relatively slow (18-24 h). Little digestion occurs in the colon but salt and water are absorbed.

Colonic Motility

The motility of the colon is in some ways similar to that found in the small intestine. The colon is inactive for a large proportion of the time but when contractions occur they may be either of a *segmental* or *peristaltic* nature. The segmental contractions have a slower frequency (3-4 per min) than in the small intestine and the deep but restricted infoldings of the wall form distinct pouches called *haustra.* This movement slowly mixes the luminal contents and improves absorption.

Propulsive activity, *mass movement,* occur infrequently (2-3 times each day) and result in the development of relatively high pressures (80-100 mmHg) that drive part of the colonic contents towards the rectum. These contraction may travel 30 cm or more.

Defaecation

The rectum is normally empty but its distension by the mass movement of faecal material from the colon induces relaxation of the smooth muscle of the *internal anal sphincter* and the urge to defaecate. In paraplegics this and the contraction of the rectum will lead to automatic defaecation but in normal people contraction of the *external anal sphincter,* which contains skeletal muscle, allows retention of the rectal contents. When conditions permit, voluntary relaxation of the external sphincter allows defaecation to proceed. The expulsion of the faecal mass may be assisted by raising the intra-abdominal pressure as a result of forced expiratory movement against a closed glottis.

Control of Colonic and Rectal Motility

The motility of the colon is largely dependent on *myogenic* and *neural* mechanisms. Slow waves are propagated through the muscle layers but their activity has less directional coordination than that in the stomach and small intestine. Indeed, reverse slow wave activity and contractions can be recorded in the distal colon. The intrinsic nervous plexus plays an important role in the coordination and conduction of contractions as distension can induce coordinated local peristalsis. Loss of the plexus (as in Hirschprung's and in Chagas' disease) results in pronounced colonic distension. The motility of the colon is also influenced by the extrinsic nerve supply as illustrated by the *gastro-colic* and *duodeno-colic* reflexes which stimulate motility after material has entered the stomach or duodenum respectively. Mass movements may follow such reflex activity and result in the urge to defaecate.

Defaecation is normally a voluntary act involving higher centres of the brain and also the medulla and spinal cord. Rectal distension causes the rectal muscle to contract and the internal anal sphincter to relax. These actions involve intrinsic and extrinsic cholinergic pathways and, in the case of relaxation, also non-adrenergic inhibitory fibres. Afferent impulses from the rectum pass to the sacral cord and higher centres. Depending on the situation, the higher centres will either augment or inhibit the sacral centre. If defaecation proceeds, the parasympathetic discharge along the pelvic nerves to the colon and rectum is augmented and the somatic motor activity in the pudendal nerve to the external anal sphincter ceases. This defaecation reflex is facilitated by the tactile stimulation which accompanies passage of the faeces through the anus.

14.3 Secretions of the Digestive System

There are five major secretory tissues in the digestive system - the *salivary glands,* the *stomach,* the *pancreas,* the *hepatic-biliary system* and the *intestine.*

Salivary Secretions

In man three pairs of salivary glands are found - the *parotid, submandibular* and *sublingual.* There are also numerous small mucus-secreting glands throughout the mouth and pharynx. In the salivary glands acini containing secretory cells drain into ducts which coalesce and finally open into the oral cavity.

About 1.5 L of saliva is secreted per day, of which one-quarter comes from the submandibular glands and two-thirds from the parotids. Secretion occurs at a continuous basal rate of 0.3 mL per minute but when stimulated by acidic foods, such as lemon juice, it can reach a maximum flow of 4-5 mL per minute.

Saliva contains a *mucous secretion* mainly from the sublingual and submandibular glands and a *serous secretion* of water and ions mainly from the parotid and submandibular glands. It also contains an enzyme, *alpha-amylase (ptyalin),* secreted by the parotid gland. Other substances found in the saliva are lysozyme, immunoglobulin A and blood group antigens.

Functions of Saliva

The water, salts and protein secreted by the salivary glands serve several functions. Water and mucin form a *lubricant* that moistens food, helps swallowing and aids in speech. In addition, the water facilitates *taste* by partially dissolving ingested material. Saliva helps in the maintenance of oral epithelium and teeth by preventing epithelial dehydration and inhibiting the proliferation of bacteria. The bactericidal effect of the enzyme lysozyme may contribute to the latter effect. Dental caries is also inhibited by salivary bicarbonate which neutralizes residual acid (ingested or produced by oral bacteria).

The digestion of carbohydrates is initiated in the mouth by the secretion of salivary alpha-amylase. But the rapid passage of food through the mouth and oesophagus means that little digestion of carbohydrate occurs before it reaches the stomach. The effectiveness of the

amylase depends on its dispersion through the food bolus and the rapidity of its inactivation by gastric acid. Estimates of its effectiveness range from 5-50%.

Formation of Saliva

The serous secretion entering the mouth is hyposmotic when compared with plasma and has less Na+ and Cl- but more K+ and HCO_3- than plasma. A primary secretion is formed in the glands by metabolically-dependent transport mechanisms which move ions from blood to acinar lumen. This secretion is probably an isosomotic, relatively protein-free secretion with an ionic composition similar to plasma but containing elevated concentrations of K+ and bicarbonate. As this primary secretion passes through the ducts, Na+, Cl- and bicarbonate are reabsorbed into the blood and K+ is secreted. Since the duct epithelium has a low hydraulic conductivity, the reabsorbed ions are not accompanied by water and so a hyposmotic secretion is produced. The actual composition of the serous secretion varies with the flow rate; the higher the rate the closer the ionic composition is to that of the primary secretion. Note that Na+-K- exchange in the ducts is stimulated by aldosterone, a hormone involved in electrolyte balance.

Control of Salivary Secretions

Increases in salivary flow may result from stimulation of receptors in the mouth, pharynx and oesophagus. Food in the mouth stimulates taste receptors and irritates the oral mucosa while chewing activates a variety of mechanoreceptors, such as pressure receptors adjacent to teeth and the muscle spindles of masticatory muscles.

These increases in salivation are reflex actions controlled *solely* by nervous activity. Afferent sensory fibres carry information to *'salivatory' centres* in the pons and medulla of the brain while efferent autonomic fibres supply the glands. The salivatory centres also receive impulses from 'higher' centres of the brain and so the sight, smell and thought of food may also cause salivation. In contrast to their actions in other viscera the parasympathetic and sympathetic fibres have a similar, but not identical effect in salivation. *Parasympathetic* stimulation, which is of major importance in man, causes a prolonged copious secretion accompanied by vasodilatation. The vasodilatation may be an indirect effect due to the release of an enzyme, kallikrein, which converts a plasma protein to the potent vasodilator, bradykinin. *Sympathetic* stimulation produces a small quantity of thick mucous saliva which is accompanied by vasoconstriction.

Gastric Secretions

The fundus and antrum are the major secretory regions of the stomach. Tubular glands in the mucosa of these regions secrete the gastric juice containing pepsinogens, acid and mucus. In the fundic mucosa *chief cells* secreting *pepsinogens* tend to lie deep within the gland and *oxyntic (parietal) cells* secreting *acid* lie closer to the gland opening. The glands secrete into numerous gastric pits ($100/mm^2$) which drain into the stomach. The pits, the glands and the remaining mucosa contain large numbers of *mucus-secreting* cells. Surface epithelial cells lying between the pits produce a bicarbonate rich secretion. The antral glands are essentially free of oxyntic and chief cells.

In total 2-3 L of an isosmotic gastric juice is secreted each day. At rest the stomach secretes a bicarbonate-rich isosmotic fluid at the rate of 15-20 mL/h but with the appropriate stimuli the stomach secretes gastric juice at rates which may exceed 150 ml/h. These stimulates secretions contain acid, pepsinogens, mucus, ions and intrinsic factor.

Function of Gastric Secretions

Gastric *hydrochloric acid* is produced by the oxyntic cells as an isosmotic fluid (150 mmol/L HCL, pH 0.8). This secretion mixes with fluid within the stomach so that the final acid concentration of the gastric contents is somewhat lower. This acid environment is necessary for the *activation* and *optimum activity* of the gastric proteolytic enzymes, the pepsins, and it denatures ingested proteins breaking up connective tissue and cells. The acid also plays a protective role, destroying bacteria and other potential pathogens.

The *pepsins* have maximum proteolytic activities between pH 2 and 3 and are formed from precursor pepsinogens by the action of acid or by the autocatalytic action of pepsins. They initiate the *breakdown of proteins* by cleaving peptide bonds adjacent to aromatic amino acids. This results in the production of polypeptides of widely differing sizes. Note that since peptic digestion is incomplete, significant quantities of protein leave the stomach to be digested in the small intestine.

There is one non-digestive but essential component of gastric juice - *intrinsic factor*. This heat labile glycoprotein (MW 60000) is essential for absorption of *vitamin* B_{12} in the ileum. It is secreted by oxyntic cells and its concentration rises concomitantly to the acid concentration. The amount of intrinsic factor secreted in 24 h is sufficient to bind 50-200 microg of vitamin B_{12}, ten to fifty times the amount of vitamin B_{12} needed for the daily supply of the vitamin. The secretion of intrinsic factor is markedly depressed in gastric atrophy. This is associated with decreased body stores of vitamin B_{12} and results in *pernicious anaemia*.

Formation of Gastric Secretions

Mucus, ions and water make up the bulk of the gastric juice secreted by the fundus and antrum. The basal secretion is plasma-like but its composition varies with flow rate. At higher rates it is modified extensively by the secretion of acid from the fundus.

Acid (HCl) is formed by *active secretion* from oxyntic cells. The H is secreted actively into intracellular canaliculi that drain into the lumen of the gastric glands. A H-K-ATPase is involved in this secretion. The source of the H is debatable. It and OH may come from metabolism or from the dissociation of water. The OH remaining in the cell is neutralized by the H from the dissociation of carbonic acid, which is formed by the hydration of CO_2. The CO_2 is derived from cellular metabolism and from plasma and its hydration is catalysed by intracellular carbonic anhydrase. The HCO_3 liberated on dissociation of the acid passes across the basolateral membrane to the blood stream.

The Cl that accompanies H into the lumen may be transported as follows: Cl may enter the cells across the basolateral membrane either in exchange for bicarbonate or be co-

transported with N as it moves down its electrochemical gradient. Accumulation of Cl within the cell provides a favourable electrochemical gradient for its diffusion across the apical membrane from cell to lumen. Thus Cl accompanies H secretion to maintain electroneutrality and water flows down the osmotic gradient so created. The result is in an isosmotic secretion of HCl.

The high concentration gradient for H between the lumen of the stomach and the plasma (10^6:1) appears to be maintained not only by H transport but also by the general impermeability of the apical membranes and tight junctions of the mucosa. Note that the gastric mucosa is normally resistant to attack by the acid and enzymes secreted by the stomach. It is protected from acid by a mucous layer which traps beneath it bicarbonate secreted by surface cells.

Pepsinogens are synthesized, stored in granules and secreted by exocytosis as inactive precursors to avoid digestion of the chief cells.

Control of Gastric Secretions

In general, stimulation causes an increase in secretion of both acid and enzymes and is accompanied by an increase in motility and hence gastric emptying. Thus acetylcholine from postganglionic parasympathetic nerves, the hormone gastrin and also histamine from the mucosa stimulate gastric secretion and motility. These mechanisms, neural and hormonal, appear to interact. The control of gastric secretion is described classically in three phases.

Cephalic phase. Chewing and the presence of food in the mouth or pharynx stimulate gastric secretion. Receptors in these areas send information to nuclei in the pons. Efferent parasympathetic fibres in the vagus activate secretory cells in the fundus and antrum directly and also activate cells in the pylorus which liberate gastrin. This hormone in turn further stimulates the secretion of gastric juice. The pontine centres of the brain are also innervated by higher centres so that the sight, smell or thought of food may increase secretion.

Gastric phase. Stretch, products of protein digestion, and possibly changes in osmolality of the gastric contents stimulate gastric secretion. They do so by stimulating receptors in the stomach which generate impulses through either the vagal or intrinsic nerves that synapse in the myenteric or submucous plexuses. These impulses stimulate gastric secretion. In addition, gastrin, released as a result of the same stimuli, increases secretion of acid and enzymes. Gastrin release is inhibited by low intraluminal pH, thus gastric secretion is decreased as free acid accumulates. Histamine released locally in the stomach wall seems also to stimulate acid secretion in this phase. Thus blockers of histamine receptors (H_2 receptors) in the mucosa, such as cimetidine, are used to decrease the production of gastric acid in people with peptic ulcers.

Intestinal phase. Chyme entering the intestine is associated normally with a decrease in gastric secretion and motility. This negative feedback thus matches the delivery of chyme to the handling capacity of the upper small intestine and is of great physiological importance. A decreased pH, fat and hyperosmolality in the duodenum cause the suppression of gastric activity and also inhibit gastric emptying. This is largely hormonally-mediated and a variety of hormones released from the intestine, including secretin, cholecystokinin (CCK) and gastric

inhibitory polypeptide (GIP), have been implicated. A role attributed in the past to a hypothetical hormone, enterogastrone, may reflect the effects of a combination of these and other substances. Of less overall importance, hormones, possibly gastrin liberated from he duodenal mucosa, may be involved in the continuation of acid secretion, albeit at a reduced rate, during the intestinal phase.

Pancreatic Exocrine Secretions

The digestive secretions of the pancreas are initially formed in acini which are similar to those in salivary glands. A system of ducts from the acini unite with the bile duct to form a common duct which enters the upper duodenum. The entrance of this common duct into the duodenum is controlled by the *sphincter of Oddi.*

The pancreas secretes about 1 litre of fluid each dy. At rest (low flow rates) the secretion is plasma-like. With higher flow rates an *alkaline fluid* rich in bicarbonates is secreted. With the appropriate stimulus the pancreas will also secrete *hydrolytic enzymes* that act on all the major groups of nutrients.

Functions of Pancreatic Secretions

The bicarbonate rich-secretion of the pancreas and also, to an extent, of the liver contributes to the neutralization of the acid chyme, which enters the duodenum from the stomach. Thus a favourable pH is established for the pancreatic enzymes which have optimal activities in the 6.7-9.0 range.

The pancreatic enzymes or their precursors are secreted along with he aqueous secretion and include:

(i) *Protease precursors - trypsinogen, chymotrypsinogen* and *procarboxypeptidases* - which are secreted by the pancreas and activated in the small intestine. The activation is initiated by the conversion of trypsinogen to trypsin by the intestinal enzyme, *enterokinase,* found on the apical plasma membranes of the intestinal epithelial cells. The trypsin in turn activates trypsinogen autocatalytically and also activates the other precursors.

(ii) An active *alpha-amylase* which is similar to the salivary alpha-amylase and splits alpha-1,4-glycosidic bonds and hydrolyses starch to mainly maltose.

(iii) *Lipases* which act on triglycerides and phospholipids.

(iv) A number of other enzymes, i.e., *ribonuclease, elastase* and *collagenase,* that act on specific macromolecules.

Formation of Pancreatic Secretions

Two group of cells contribute to the secretion - the acinar cells and the duct cells. The acinar cells, as well as secreting the enzyme precursors by a Ca-dependent exocytic mechanism, also secretes Cl. Cl secretion is followed by the movement of Na and H_2O

through the paracellular pathway which is relatively leaky. Secretion from these cells is stimulated by cholecystokinin (CCK). The duct cells, in contrast, secrete bicarbonates. Again Na and water follow across the leaky paracellular pathway. Secretion is stimulated by secretion probably via a cyclic AMP-mediated mechanism.

The enzymes of the pancreatic secretions are all synthesized in the same cells and released in parallel. However, the ration is not necessarily constant and examination of the pancreatic secretions of individuals on widely differing diets (i.e., high protein or carbohydrate) shows that these secretions can change to suit the diet.

Control of Pancreatic Secretions

A *cephalic phase* may be recognized during which pancreatic secretion is stimulated by vagal activity. The early phase of secretion is supplemented by the release of gastrin from the antrum during the *gastric phase* of digestion. The major control is, however, exerted during the *intestinal phase* when nerves and, more importantly, intestinal hormones determine pancreatic control.

The entry of chyme into the duodenum is generally followed by the secretion of a bicarbonate and enzyme-rich fluid from the pancreas. The hormones mostly responsible for this secretion are secretin and CCK. *Secretin* (and a small quantity of CCK) is released from the mucosa of the duodenum and upper jejunum in response to *acid* chyme. It acts on the duct cells and stimulates secretions of the bicarbonate-rich fluid. The release of CCK is stimulated by the *products of digestion* in the upper small intestine. It stimulates an enzyme-rich secretion from acinar cells.

Biliary Secretions

Bile is produced in the *liver* and stored and concentrated in the *gall-bladder*. Bile contains both *secretory* products important in digestion and *excretory* products, such as bile pigments and cholesterol, and also certain hormones and drugs which are either metabolized or conjugated within the hepatic cells. Bile is initially secreted by the *hepatic cells* into the *bile canaliculi*. From there it passes to the larger ducts which drain each liver lobule and then to the main ducts and common ducts. The cystic duct from the gall-bladder joins with the common duct before it enters the duodenum.

About 1 litre of bile is secreted each day. It is produced continuously but between meals the contraction of the sphincter of Oddi causes it to accumulate in the gall-bladder (volume 20-50 mL). In the gall-bladder an isosmotic electrolyte solution is reabsorbed leaving behind a concentrated solution of bile salts, bile pigments, lecithin and cholesterol. Too much cholesterol or insufficient bile salts or lecithin in bile can result in the precipitation of cholesterol and the formation of *gall-stones.* Bile is ejected by contraction of the gall-bladder and enters the duodenum after relaxation of the sphincter of Oddi. The bile contains two components which are important in digestion, namely, *bile salts* (salts of chenodeoxycholic acid and cholic acid) and *bicarbonate.* The remainder is largely bile pigments, other ions and water.

Functions of Biliary Secretions

The bicarbonate secreted by the liver aids in the *neutralization* of acid chyme which enters the duodenum from the stomach. The bile salts are important in the *digestion* and *absorption of fats* and in the *absorption of fat-soluble vitamins.* Their role in fat digestion and absorption can largely be attributed to (i) their emulsifying action - particularly in the presence of lecithin and monoglycerides - and (ii) the ability of conjugated bile acids to lower the optimum pH of pancreatic lipase from approximately 9.0 to 6.7.

Formation of Biliary Secretions

At rest the liver secretes a plasma-like fluid containing the bile acids and bile pigments. The mechanisms involved in this secretion are not understood. Bile pigments (mainly bilirubin) are derived principally from the breakdown of haemoglobin, myoglobin and cytochromes and are a waste product. The duct cells secrete a bicarbonate-rich solution by a mechanism which may be similar to that in the pancreatic duct cells.

The bile acids (cholic and chenodeoxycholic acids in man) are synthesized in the liver from cholesterol at a rate of about 0.5 g per day and are conjugated with glycine or taurine. The conjugated bile acid then combines with Na to form a bile salt. Conjugation has two advantages: it increases their solubility at low pH and it largely limits passive absorption of the bile acids in the upper small intestine. The bile salts are concentrated in the gall-bladder by active reabsorption of Na. As water follows passively, the bile salts are concentrated about three-fold depending on the time between meals. However, because the sodium salts of the bile acids form relatively large aggregates (micelles), the osmolality of gall-bladder bile is not substantially greater than that of plasma.

Control of Biliary Secretions

Biliary secretion is controlled by autonomic nerves and circulating hormones and by bile salts delivered to the liver by the portal circulation.

Nervous control plays only a minor role in regulating biliary secretion. Activity in postganglionic parasympathetic fibres produces a small increase in secretion whereas activity in sympathetic splanchnic nerves causes vasoconstriction and a decrease in secretion.

Hormonal control of biliary secretion is exerted largely by secretin, cholecystokinin (CCK) and gastrin. *Secretin,* released as a result of acid chyme in the duodenum, increases the production of bicarbonate-rich secretion from the duct cells (as in the pancreas). CCK released as a result of fats and peptides in the duodenum, causes contraction of the gall-bladder. *Gastrin* has a similar action. These hormones (CCK and gastrin) may also stimulate the secretion of bile salts but their importance in this role is in doubt.

The most potent stimulators (cholemetics) of bile salt secretion are the *bile salts themselves.* Approximately 90% of the salts secreted into the small intestine are actively reabsorbed in the terminal ileum and returned to the liver in the portal circulation. This

circulation of the bile salts is economic in that the pool of bile salts (about 0.4 g) is recycled as much as six to eight times in a 24 h period.

Intestinal Secretions

As well as mucus-secreting cells which are found throughout the intestinal tract, Brunner's glands in the *duodenum* produce a highly viscid secretion which may serve to trap alkaline (bicarbonate-rich) fluid secreted by the duodenal cells at the surface. This may protect duodenum from the acid chyme entering from the stomach. The rate of secretion is increased by parasympathetic activity and by secretin.

In the jejunum and ileum there is also the variable secretion (perhaps 2 L or so) of an isosmotic NaCl solution from the intestinal crypt cells. The cells here accumulate Cl from the interstitial fluid which then diffuses from the cells to the lumen. The leaky paracellular pathway allows Na and water to follow readily. This secretion is stimulated by cyclic AMP. A variety of bacterial endotoxins (cholera toxin, toxins from some strains of *E. coli*) can activate this secretory process causing diarrhoea.

Fluid collected from the small intestine, in the absence of gastric, pancreatic and biliary secretions, contains a variety of enzymes. Many of these, i.e., aminopeptidases, amylases and phosphatases, are important in the digestive process and are found in the brush-border region. They are not, however, intestinal secretions but are released from desquamated intestinal cells.

In the colon, mucus and a small volume of alkaline solution rich in bicarbonates are produced. This may involve an bicarbonate-chloride exchange so that the colonic contents are higher in bicarbonates than plasma but lower in chlorides. However some of the bicarbonate may be neutralized by organic acids in the lumen. In addition, there is a Na-K exchange which results in the colonic contents being rich in K. This exchange is enhanced by aldosterone.

14.4 Gastrointestinal Hormones

The gastrointestinal hormones are *peptides* produced by enterochromaffin cells in the GIT mucosa and are involved in the control of GIT motility and secretion. These cells are related to those endocrine cells (i.e., adrenal medulla) which are of neuroectodermal origin and are sometimes referred to as APUD cells (Amine content, Precursor Uptake, ability to Decarboxylate). A number of these GIT peptides are also found in central and peripheral neurones where they may function as neurotransmitters.

Gastrin, cholecystokinin (CCK), secretin and *gastric inhibitory polypeptide (GIP)* fulfil the criteria necessary to establish their importance as regulators of GIT function under physiologic conditions, namely:

1. The physiologic stimulus involving the postulated hormone (i.e., one arising as a result of the intake of food) applied to one part of the gut must change the activity at the another part.

2. This change must persist after all nervous connections between the two parts have been interrupted.

3. A substance isolated from the part of the gut to which the stimulus was applied, must, when purified and injected into the blood, mimic the effects of the physiologic stimulus.

4. This substance must be identified chemically.

There are other peptides of gastrointestinal origin that may be important, i.e., vasoactive intestinal peptide (VIP), motilin, bulbogastrone, eneteroglucagon, and somatostatin, but as yet they do not fulfil all of these criteria.

The GIT peptides can be classified on the basis of their chemical structure into two groups: (i) gastrin and CCK, the five amino acids at the carboxyl end of which are identical, and (ii) secretin, GIP, VIP, (also glucagon) which have sequences of amino acids in common. Because of their structural similarity gastrin and CCK may interact at the same receptor site. The result will depend on the concentration of the hormones, on their affinity for the receptor and their efficacy in activating the target cell. Thus the combined effects of gastrin and CCK may be additive or, if one hormone is less effective than the other at a particular site, then its effect may appear to be inhibitory.

The endocrine cells found in the GIT mucosa are exposed on their luminal surfaces to the contents of the GIT tract and it is likely that constituents of the chyme can cause the release of their hormones into the blood stream. In addition, both intrinsic and extrinsic nervous reflexes can cause release of some of these hormones, which not only act through the bloodstream but also may diffuse locally and have so-called *paracrine* actions.

Many of the hormones, i.e., GIP, gastrin, CCK and secretin, appear to stimulate the release of insulin. The GIT hormones may have an important trophic effect on their target glands, i.e., gastrin stimulates the growth of the gastric mucosa and CCK stimulates the growth of acinar cells in the pancreas.

Gastrin

Two related gastrins, I and II, have been identified. Both are 17-amino acid chains (G17) and differ only at position 12. As well as G17 gastrin, smaller forms (G14) and larger less potent forms (G34) of gastrin (big gastrin) have been isolated from man. The properties of gastrin are determined by the terminal tetrapeptide sequence (-Try-Met-Asp-Phe-NH_2). Pentagastrin is a synthetic product containing this tetrapeptide sequence that has all the properties of gastrin but is less potent. It is used clinically to stimulate gastric secretion, for example in assessing inability to secrete HCl *(achlorhydria).*

The gastrins are produced by cells, called G cells, which are in the mucosa lining the antral region of the stomach and the upper small intestine. Gastrin is released as a result of (i) stimulation by *products of digestion* (especially peptides), caffeine and alcohol in the stomach, either as a direct effect on the cells or by local intrinsic nerve reflexes; (ii) *nervous activity* in extrinsic pathways during the cephalic phase of gastric secretion; or (iii) *local*

distension of the antral region mediated by local intrinsic nerve reflexes. Release of gastrin is inhibited by increasing gastric *acidity* and by the intestinal hormones, *secretin* and *gastric inhibitory peptide.* Gastrin may be produced by certain tumours in the GIT and this can result in marked peptic ulceration (Zollinger-Ellison syndrome).

Gastrin is carried in the blood stream and stimulates *gastric secretion of HCl, pepsinogen* and *intrinsic factor.* It enhances *gastric motility* and increases the tone of the lower oesophageal sphincter (though the latter may not be observed at physiological concentrations). It produces a small increase in pancreatic secretion and causes contraction of the gall-bladder. It also stimulates the growth of the gastric mucosa.

Cholecystokinin

Cholecystokinin (CCK), also known as pancreozymin, has the same active terminal tetrapeptide sequence as gastrin but a total chain length of 33 amino acids. Therefore, the effects of CCK and of gastrin are quantitatively similar but differ quantitatively and my be competitive. It is produced by J cells found in the mucosa lining the duodenum and jejunum. It is released into the blood as a result of stimulation by *products of digestion* (especially fats, peptides and amino acids) in the duodenum and jejunum either as a direct effect on the cells or through local intrinsic nerve reflexes.

CCK is carried in the bloodstream and stimulates *enzyme-rich secretion* from the acinar cells of the pancreas. It causes contraction of the *gall-bladder* and relaxation of the *sphincter of Oddi.* It increases *small intestinal motility* but inhibits *gastric motility.* In some species, i.e., dog, it inhibits gastric secretion but whether it does so in man is debatable. It also stimulates the growth of acinar cells in the pancreas.

Secretin

Secretin was the first hormone to be discovered by Bayliss and Starling in 1902. It contains twenty-seven amino acids. Of these fourteen occupy the same relative position as in glucagon. Its structure is unrelated to that of gastrin or CCK and it inhibits gastric acid secretion in a non-competitive way. Secretin is produced by S cells found in the mucosa lining the duodenum and jejunum. It is released into the blood as a result of *increased acidity* in the duodenum and jejunum, either via a direct effect on the cells or indirectly through local nerve reflexes.

It is carried in the bloodstream and stimulates the ducat cells in the *pancreas* and *liver* to produce increased volumes of *bicarbonate-rich secretions.* In the stomach secretin stimulates *pepsinogen* secretion and inhibits *acid* secretion by direct action on oxyntic cells and by inhibition of gastrin release.

Gastric Inhibitory Peptide

Gastric inhibitory peptide (GIP), also called glucose-dependent-insulin-releasing peptide, is a 43-amino acid polypeptide with some structural similarity to secretin. GIP is

produced by cells (K cells) found in the mucosa lining the duodenum and upper intestine. Its release into the blood is stimulated by the presence of *fat* and *glucose* in the upper intestine.

GIP travels in the bloodstream and inhibits *gastric acid secretion* by a direct action on the oxyntic cells and by inhibition of gastrin release. It also inhibits *gastric motility.* It releases *insulin* from beta cells of the pancreas and may be of more physiological importance in this respect than other gastrointestinal hormones. GIP may also stimulate secretion from the small bowel.

Vasoactive Intestinal Peptide

Vasoactive intestinal peptide (VIP) contains twenty-eight amino acids and has some structural similarity to secretin. It is produced in the upper small intestine and is released into the blood, probably as a result of increased acidity in the duodenum. VIP is also found in the nervous system where it may be important as a neurotransmitter, both centrally and peripherally.

VIP released from the intestine travels in the bloodstream and stimulates secretion of serous fluid from the pancreas. It inhibits gastric acid secretion and motility. It may also cause vasodilatation in systemic arterioles. When secreted in excess, for example by a non-insulin secreting islet-cell adenoma of the pancreas, VIP can cause the 'H_2O-diarrhoea' syndrome.

Other Intestinal Peptides

Other intestinal peptides may also play roles as hormones, for example, *motilin, bulbogastrone, enteroglucagon* and *somatostatin.* Motilin is produced by the mucosa of the duodenum and jejunum and it may increase motility in the stomach. It is probable that the functions ascribed to enterogastrone, i.e., inhibition of gastric motility and secretion when fat is present in the duodenum, are in fact a reflection of the effects of GIP, of inhibitory nerve reflexes, or of the combined action of other hormones.

The *prostaglandins* are synthesized, released and degraded in the GIT and when ingested or injected may influence its function, but their role in the normal physiology of the tract remains debatable.

14.5 Absorption

Absorption may be defined as the net passage of a substance from the lumen of the gut across the epithelium to the interstitial fluid. Two important factors influencing absorption are the available *surface area* and the *flux* of molecules across the epithelium, i.e.,

amount/min = area x flux (amount/min/unit area)

In the gut the *surface area* available for absorption is greatly expanded by *loops or coils* of the gut, by *mucosal infoldings* which increase the surface area of the loops by some three-fold, by *villi* which further increase the surface area some thirty-fold, and by *microvilli* which form the brush borders of the luminal surface of the cells and increase the available

surface area some 600-fold. In the gut of an adult man the total surface area available for absorption is approximately $2x10^6$ cm^2, which is equivalent to a hundred times the external surface area of the body.

The *flux* of molecules across the epithelium depends on their ability to penetrate the epithelial membranes and also on the driving force for their transport, i.e., their electrochemical potential gradient. The rate of *penetration* of the epithelium depends on the properties of the substance to be absorbed and on the nature of the epithelial barrier. The ability of a substance to cross the epithelium will depend on its *lipid solubility*, its *size*, and on the presence of specific *carrier molecules* in the membrane. Carrier-mediated transport may be 'downhill', i.e., facilitated diffusion, or 'uphill', i.e., active transport, co-transport or counter-transport. Furthermore, the leakier the paracellular pathway between the epithelial cells then the more readily solutes of small relative molecular mass, ions and water can cross the epithelium.

The *concentration* of many substances in the lumen will be determined by their rate of *digestion.* Absorption will also depend on the time in contact with the absorptive surfaces and so control of *motility* is essential to allow normal absorption to take place. The concentration of the products of digestion in the interstitial fluid will depend on their rate of *removal* by the blood, which will depend on the blood flow. The blood vessels in the villi are arranged in loops so that the distance for diffusion in the interstitial fluid from the basolateral epithelial plasma membrane to the capillaries is minimized. The volume of blood flowing to the GIT represents 20-30% of the cardiac output at rest. The rate of capillary blood flow is a thousand time greater than that of the lymphatic flow. Thus substances such as glucose, amino acids, ions and water, which readily enter the capillaries, are removed in them and pass through the portal circulation to the liver. Only those substances, chylomicrons (small lipid aggregations), which do not readily cross the capillary basement membrane are transported predominantly by the *lymphatic* circulation. Such substances enter the venous blood via the thoracic duct and are thus not exclusively transported directly to the liver after absorption. There is some recent evidence which suggests that the hydrostatic pressure in the capillaries in the villi is less than the plasma colloid osmotic pressure. If this is so, it indicates that the driving force for fluid movements in the villi always favours net absorption from the interstitial fluid to the plasma and that ultrafiltration does not normally occur across the capillaries. Therefore, absorption of water and solutes from the gut lumen will be favoured.

Some lipid-soluble drugs can be administered by placing them either under the tongue or next to the cheek.

Absorption in the Stomach

In the stomach the H concentration is maintained at a concentration up to one million times greater than that in the plasma while the Na concentration is as low as one-tenth of that in the plasma. This implies the existence of a *gastric mucosal barrier* in which both the apical plasma membranes of the epithelial cells and the 'tight' junctions between these cells are very impermeable to ions. It is not surprising, therefore, that *little* absorption normally occurs in the stomach. However, lipid-soluble substances, i.e., alcohol and organic acids such as

acetylsalicylic acid in their non-ionized form, are absorbed to some extent across the stomach wall.

A number of agents can disrupt the gastric mucosal barrier. These include bile salts, short-chain fatty acids, acetylsalicylic acid, ethanol and perhaps corticosteroids. This has important clinical implications, for the entry of H into the interstitial fluid acidifies the fluid and leads to damage to the epithelial cells and to the underlying capillaries resulting in local haemorrhage. Such acute ulceration may progress to chronic ulceration.

Absorption in the Intestine

The products of digestion are absorbed predominantly in the small intestine. Absorption of salt and water occurs in the small intestine and also in the large intestine.

Sodium

Under normal conditions, up to about 1 mol of Na (equivalent to 58 g of NaCl) is absorbed per day. Only about one-sixth of this is derived from the diet, the remaining five-sixths having been secreted into the GIT. Since total exchangeable body Na is approximately 3 mol, the importance of Na absorption is obvious, as is the rapid depletion of ECF volume if Na is lost from the gut in severe vomiting or diarrhoea. Approximately 5-10 mmol Na is excreted in the faeces daily.

About 90% of Na absorption occurs in the *small intestine.* The remaining 10% occurs in the *large intestine.* Absorption is thought to occur across the mature cells at the tops of the villi. Absorption from the large intestine is modified by *aldosterone,* which stimulates the uptake of Na in exchange for K which is secreted. Na absorption is an *active process* involving passive entry of Na from the lumen to the cell and active transport from the cell to the interstitial fluid. Note that in the small intestine in particular, the paracellular pathway is 'leaky' and therefore considerable passive movements occur between the gut lumen and the interstitial fluid. These movements contribute to the rapid equilibration of luminal contents with interstitial fluid. Thus luminal fluid quickly becomes isosmotic with plasma.

Na absorption in the small intestine, but not in the colon, is increased by *glucose* and *amino acids* in the lumen, reflecting co-transport. Na and glucose, and Na and amino acids, appear to share common carriers for cellular entry from the lumen. It is believed that under normal circumstances this entry is driven by Na diffusing down its electrochemical potential gradient thereby carrying sugar or amino acids into the cell. This coupling of Na and organic solute movements has important therapeutic implications in the management of cholera and other secretory diarrhoeas. In such cases the increased net Na, Cl and water secretion can be offset by stimulating Na absorption with glucose taken orally.

Potassium

K is *absorbed throughout* the intestinal tract but whether this process is active, involving K movement through the cells, or passive, through a paracellular pathway, is unclear. K may also be *secreted.* Again the mechanism is controversial. It may reflect net

movement from blood to lumen through the paracellular pathway and down the electrical gradient generated by Na absorption, although there is evidence in the colon for a cellular pathway. In the colon K secretion is stimulated by Na in the lumen and is increased by *aldosterone.*

Chloride and Bicarbonate

Cl absorption may result from the electrical gradient generated by active Na absorption. In addition, in the small intestine Cl may be co-transported by a carrier mechanism into the epithelial cells with Na, the movement being driven by the Na gradient. In the *ileum* and *colon* Cl can be absorbed in exchange for bicarbonate which is secreted. A the bases of crypts of the villi Cl is secreted, not absorbed.

Calcium

Ca absorption from the intestine occurs largely in the *duodenum* and is regulated by the hormone, 1,25-dihydrocholecalciferol (1,25-DHCC), which stimulates Ca entry to the cells from the lumen. The mechanism involved, however, is not understood. Ca entry may be carrier-mediated and there have been claims for the presence of a Ca-ATPase in the brush border suggesting that such uptake might be an active process. A Ca-ATPase has also been identified in the basolateral membrane and Ca extrusion from the cell to the interstitial fluid is probably an active process. A Ca-binding protein has been isolated from intestinal epithelia but its relationship to Ca transport remains to be clarified.

Iron

Normally 1 to 2 mg of iron is absorbed per day, equivalent to the daily loss from the body. Most of this absorption takes place in the *duodenum.* Factors affecting iron absorption include (i) the state of the iron, i.e., iron complexed to haem is more readily absorbed than inorganic iron, and, of inorganic iron, the ferrous form is more readily absorbed than the ferric, (ii) the presence of dietary constituents, i.e., ascorbic acid and possibly intrinsic factor which aid absorption, (iv) bicarbonates in the duodenum which inhibits absorption, (v) a variety of substances, including tannate, phosphate and phylates which forms complexes with iron thus preventing absorption, and (vi) the quantity of iron in the epithelial cells. Iron in these cells may be present either as ferritin, whose role in iron absorption is controversial, or in a separate pool perhaps related to an iron-binding protein. It appears that epithelial cells produced in the crypts of the villi when plasma levels of iron are low have a low iron content and a high absorptive capacity. Thus the absorption of iron after a haemorrhage may be delayed 3-4 days until such cells are produced and migrate up the villi. However, what regulates the epithelial cell iron content remains to be established. Iron is normally lost from the body when the epithelial cells are desquamated and destroyed in the intestine. Iron is unusual in that its content in the body is regulated by controlling absorption from the gut rather than excretion through the kidneys.

Water

Of the approximately 10 L of water absorbed per day, about 8 L (20% of total body water) has been secreted into the GIT. Approximately 90% of the water absorption occurs in

the *small intestine* with only about 1 L absorbed in the colon, leaving 0.1 L to be excreted in the faeces. As much as 5 L of water can be absorbed by the colon per day.

There are rapid movements of water across the small intestine in response to osmotic gradients. Ions also move freely through the 'tight' junctions. Thus the luminal contents rapidly attain the osmolality of the interstitial fluid. Throughout the intestine water absorption from an isosmotic luminal solution is secondary to *solute* absorption and is driven by the resulting osmotic gradient. The coupling of solute and water absorption probably occurs within the lateral intercellular spaces. Movement of this absorbed water from the interstitial fluid to the capillaries is driven by the plasma colloid osmotic pressure as expected. Changes in the capillary hydrostatic or plasma colloid osmotic pressure may influence net water movement between blood and lumen.

Sugars

There are absorbed almost entirely as monosaccharides, the final conversion from the di- to the monosaccharide involving disaccharidases in the brush border of the epithelial cells themselves. Monosaccharides are largely absorbed in the *duodenum* and *upper jejunum.* The rate of absorption of glucose (and galactose which competes with glucose for the co-transport carrier) is greatly influenced by Na in the lumen. Na and glucose appear to share a common mode of entry from lumen to cell, the diffusion of Na down its chemical gradient providing he driving force for glucose entry into the cell which may be against its concentration gradient. The absorbed monosaccharides seem not to be metabolized by the cells but diffuse from them to the interstitial fluid and then to capillaries.

Proteins

Before absorption takes place, the proteins are broken down to peptides or amino acids. About 50% of the digested protein comes from ingested food, 25% from proteins in the gut secretions and 25% from desquamated epithelial cells. Gastric and pancreatic enzymes hydrolyse protein to short-chain peptides (up to residues long) which are further hydrolysed at the brush border to free amino acids or to smaller peptides (MW < 250) which enter the intestinal mucosa. Absorption normally occurs in the *duodenum* and *upper jejunum.* Amino acid absorption, like sugar absorption, seems to be increased by luminal Na. There seem to be at least four specific mechanisms by which amino acids are absorbed: one for neutral amino acids, one for basic amino acids, one for acidic amino acids and one for the imino acids (proline, sarcosine). Di- and tripeptides may be absorbed from the lumen as such and are hydrolysed within the epithelial cells. In neonates, antibodies and other proteins contained in colostrum my be absorbed in their intact form by pinocytosis.

Lipids

The dietary lipids, up to 150 g per day, are primarily triglycerides, phospholipids, cholesterol and plant steroids. The absorption of lipid is normally an efficient process, the faeces containing less than 5 g fat per day. It occurs in number of stages:

(i) *Digestion and micelle formation.* Large lipid droplets must be converted to small lipid droplets and these stabilized to prevent coalescence. This process of *emulsification* requires a shearing force provided by intestinal motility and the presence of stabilizers, of which the physiologically most important are *bile salts.* Pancreatic *lipase* acting at the oil-water interface of the emulsion converts triglycerides to free fatty acids and 2-monoglycerides. These, together with bile salts, lecithin, cholesterol and fat-soluble vitamins, form *micelles.* Micelles are small aggregations (4-6 nm in diameter) of about twenty fat molecules whose hydrocarbon chins interdigitate within a fluid interior and whose polar groups form a negatively charged spherical shell surrounded by cations in aqueous solution.

(ii) *Passage from lumen to cell.* It is believed that the micelles diffuse to the apical cellular membranes and then free fatty acids and monoglycerides leave the micelles and diffuse across the apical membrane. The micelles themselves do not cross the membrane. The bile salts are not absorbed to any extent in the duodenum or jejunum. Absorption occurs in the terminal ileum and involves a carrier-mediated active process.

(iii) *Cellular metabolism and synthesis of chylomicrons.* The lipid crossing the brush borders of the epithelial cells is transferred to the endoplasmic reticulum. Fatty acids may pass as water-soluble coenzyme A derivatives. Alternatively it has been suggested that binding to a soluble protein may facilitate their passage. Within the endoplasmic reticulum fatty acids are re-esterified to triglycerides. Then chylomicrons are assembled in the region of the Golgi apparatus of the cells. *Chylomicrons* are complexes, about 100 nm in diameter, of triglycerides (87%), cholesterol esters (3%) and fat-soluble vitamins, all of which are enveloped in a hydrophobic coat composed of a specific apolipoprotein B (1%), phospholipid (9%) and free cholesterol.

(iv) *Passage from cell to interstitium.* The release of the chylomicrons from the cell occurs by poorly understood mechanisms which may involve exocytosis.

(v) *Removal by the lymphatic system.* The chylomicrons enter the lymphatic system via the lacteals in the villi. Removal occurs by the lymphatic system rather than by the blood capillaries because the former is permeable to the chylomicrons, perhaps reflecting a lack of tight junctions between the endothelial cells of the terminal lymphatics. The chylomicrons pass through the lymphatic system to the systemic circulation via the thoracic duct. In the blood the chylomicrons bind apolipoprotein C, derived from high density lipoproteins (HDL), to their coat. The triglyceride component (87%) of the chylomicrons is taken up by adipose tissue and muscle, whereas the cholesterol component (3% of total) passes on through the circulation to enter liver cells.

In contrast, short- to medium-chain fatty acids (< 12 carbons) are absorbed from the lumen without requiring prior hydrolysis or micelle formation and tend not to be re-esterified within the epithelial cells. They pass into the capillaries where they bind to albumin, and thence into the portal circulation rather than into the lymphatics.

Vitamins

The pathway followed by vitamins during absorption from the GIT is to a large extent dependent on their lipid and water solubilities. he *fat-soluble vitamins (A, D, E and K)* and their precursors are incorporated into micelles from which they diffuse into the epithelial cells. Like the dietary lipids the absorption of these vitamins is dependent on the presence of adequate bile salts.

The absorption of many *water-soluble* vitamins is facilitated by the presence of specific metabolic-dependent carriers. In some cases these uptake processes show a Na dependence similar to that for the uptake of amino acids and sugar.

The absorption of *vitamin* B_{12} is further specialized in that it requires the formation of a vitamin-intrinsic factor complex. The intrinsic factor, a glycoprotein secreted by the oxyntic cells of the gastric epithelium, is absorbed along with the vitamin by a pinocytic mechanism. This mechanism is facilitated by luminal Ca or Mg at an alkaline pH. Within the epithelial cells the complex is dissociated and the vitamin passes from the cells to the interstitial fluid.