DIGESTION & ABSORPTION

• proteins, fats and complex CHO are broken down, digested, principally in the small intestine
• the products of this digestion, plus the vitamins and minerals cross the mucosa and enter the portal blood or lymph, absorption
• orderly process, involving a large number of digestive enzymes, originating in the saliva, stomach, SI and exocrine pancreas
• the action of these enzymes is aided by the action of HCl in the stomach and by bile in the SI

• the mucosa of the SI has a brush border made of numerous microvilli
• this is covered by a layer of neutral and amino-sugars, the glycocalyx
• the membranes of the mucosal cells contain glycoprotein enzymes which hydrolyze CHO and peptides
• the glycocalyx is made, in part, of the CHO portions of these glycoproteins which extend into the intestinal lumen
• next to the brush border and the glycocalyx is a 100-400 μm unstirred water layer (UWL)
• the mucous coat overlying the mucosa is also a significant barrier to difusion
• processes involved in the absorption of substances include,

a. diffusion
b. facilitated diffusion
c. solvent drag
d. active transport
e. secondary active transport
f. endocytosis

Carbohydrates CHO

Digestion

• the principal dietary CHO is composed of,

a. polysaccharides
b. monosaccharides
c. disaccharides

• starches, polymers of glucose and their derivatives, are the only polysaccharides of importance to humans
• in glycogen, glucose molecules are joined by 1-4~ linkages, with some chain branching by 1-6α linkages
• amylopectin, which ~ 80-90% of dietary starch, is similar but has less branches
• amylose possesses only 1-4~ linkages and is a straight chain
• glycogen is found in animals, whereas the later two are of plant origin
• the disaccharides lactose & sucrose are also ingested, along with the monosaccharides glucose & fructose
• starch is first degraded by ptyalin, the α-amylase of saliva
• however, the optimal pH for this is 6.7 and activity is terminated by gastric acidity
• once in the SI, pancreatic α-amylase is added
• both of these attack the 1-4α linkages but spare,

a. the 1-6α linkages
b. the 1-4α linkages next to branch points
c. the terminal 1-4α linkages

• thus, the end products of this digestion are,

a. the disaccharide maltose
b. the trisaccharide maltotriose
c. larger polymers of glucose with 1-4α linkages
d. branched polymers, ~ 8 units, the α-limit dextrins

• these are further digested by the oligosaccharidases located at the outer portion of the membrane of the microvilli,

a. maltase
b. lactase
c. sucrase
d. α-limit dextrinase

• in many mammals and some races of humans, intestinal lactase activity is high at birth, declines to low levels in childhood and remains low subsequently

• low levels being associated with intolerance of milk as lactose remains in the GIT and acts as an osmotic agent prior to being broken down by bacteria in the colon
• however, most Caucasians retain their lactase activity but most adult blacks are intolerant

■ ***Absorption***

• hexoses and pentoses are rapidly absorbed across the intestinal mucosa
• these then enter the capillaries which drain to the portal vein
• glucose and Na^+ share the same symport, thus a high [Na] at the mucosal surface facilitates glucose absorption
• due to the action of the basal Na-K-pump → ***secondary active transport***
• the same mechanism also transports galactose
• fructose utilizes a different carrier, and its absorption is independent of luminal Na^+
→ ***facilitated diffusion***
• insulin has minimal effect on the intestinal transport of sugars, as is the case for reabsorption in the proximal nephron
• both are essentially normal in diabetes but are depressed by the drug phlorhizin
• the maximal rate of glucose absorption is **~ 120 g/h**

Proteins & Nucleic Acids

Protein Digestion

• begins in the stomach, where pepsins cleave some of the peptide linkages
• these are secreted in an inactive form, as ***pepsinogens***, and are activated by the low luminal pH
• there are a large number of these, however, they can be divided into two distinct immunohistochemical groups,

a. pepsinogen I - found only is HCl secreting region
b. pepsinogen II - also found in the pyloric region

• maximal acid secretion correlates with pepsinogen I levels, and patients with high circulating levels have a 5 times higher incidence of ulceration
• pepsins hydrolyse bonds between an aromatic AA, such as tyrosine or phenylalanine, and a second AA
• thus, the products of this digestion are diverse peptides
• the optimum pH ~ 1.6-3.2, therefore action is terminated on exit from the stomach
• the pH in the duodenal cap ~ 2.0-4.0, but the rest of the duodenum is ~ 6.5

• in the SI, these smaller peptides are further fragmented by proteolytic enzymes of the pancreas, which may be divided into the,

a. endopeptidases - trypsin, chymotrypsin & elastase
b. exopeptidases - carboxydipeptidases

and the aminopeptidases of the brush border

• some di and tripeptides are absorbed and finally broken down by intracellular peptidases
• thus, the final digestion of peptides occurs in three locations,

a. the lumen
b. the brush border
c. within the cell

Absorption

• the l-AA's are absorbed more rapidly then their d-AA isomers and following a meal there is a sharp transient rise in the nitrogen content of portal blood
• the d-isomers are absorbed soley by passive diffusion
• whereas, most of the ***l-isomers*** are actively transported from the lumen
• there are 4 seperate systems,

a. neutral AA's
b. basic AA's
c. proline, hydroxyproline and glycine
d. dicarboxylic AA's - glutamic and aspartic acids

- there is a separate system for the di & tri-peptides
- transport is linked to Na^+ and is facilitated by an increase in luminal [Na], as for glucose
- from the cells, diffusion of AA's into the portal blood is passive
- absorption is rapid in the duodenum and the jejunum, but slow in the ileum
- of the digested protein,

a. ingested food → 50%

b. GIT secretions → 25%

c. desquamated mucosal cells → 25%

- only ~ 2-5% of protein in the SI escapes in the stools, most of the protein found is due to bacteria and cellular debris from the colon
- in infants moderate amounts of undigested proteins are also absorbed
- the IgG secreted in maternal milk enters the circulation by endocytosis, although this transfer is relatively minor for humans

- absorption of protein antigens takes place in large microfold cells (M cells), which are specialized epithelial cells which overly aggragates of lymphoid tissue → Peyer's patches
- these cells present the antigens to lymphoblasts, which are activated and enter the circulation
- they eventually return to the mucosa, where they secrete secretory IgA in response to exposure to the same antigen

Nucleic Acids

- pancreatic nucleases split the nucleic acids to nucleotides
- these are subsequently split in the nucleosides and phosphoric acid by enzymes at the brush border
- these are further broken down to their constituent sugars and purine and pyrimidine bases
- the bases are absorbed by active transport

Lipids

Fat Digestion

• significant digestion begins in the duodenum with pancreatic lipase being the most important
• this hydrolyses the 1 & 3 bonds of triglycerides (TG) with relative ease but the 2 bond at a slower rate
• the principal metabolites are FFA's and 2-monoglycerides
• this acts on fats which have been emulsified, but cannot act without the protein colipase, which is secreted by the pancreas
• this binds to the surface of the droplet, displacing the emulsifying agents and anchoring the lipase
• most of the dietary cholesterol is in the form of cholesterol esters, and pancreatic esterase hydrolyses these in the lumen
• fats are finely emulsified in the SI by the detergent action of the bile salts, lecithin, and monoglycerides $\rightarrow$ particles 200-5000 nm
• bile salts alone are relatively ineffective
• when the [bile salts] is high, as after a meal and gallbladder contraction, lipids and bile salts interact spontaneously to form micelles ~ 3-10 nm
• these generally contain FFA's, monoglycerides and cholesterol
• micellar formation further solubilizes the lipids and provides a mechanism for their transport to the brush border, through the UWL by diffusion
• lipids enter the cells by passive diffusion and are rapidly esterified, maintaining the concentration gradient for diffusion
• unlike the ileal mucosa the uptake of bile salts by the jejunum is low, and these diffuse back into the intestinal lumen
• thus, bile salt micelles solubilize lipids, transport them across the UWL, and maintain a saturated concentration of lipids at the mucosal cell
• pancreatectomized animals, or those with pancreatic insufficiency, suffer steatorrhoea, due to,

a. lipase deficiency
b. depressed micellar formation
   - due to low $HCO_3$from the pancreas
   - the acid environment prevents incorporation of FFA's into micelles

• this is also why patients with excess gastric acidity secrete fatty stools

Fat Absorption

• monoglycerides, cholesterol and FFA's from micelles enter the mucosa by passive diffusion
• the subsequent fate of FFA's depends upon their size,

a. FFA < 10-20C $\rightarrow$ portal blood as FFA
b. FFA > 10-12C $\rightarrow$ reesterified to TG

• in addition, some of the absorbed cholesterol is esterified
• the TG and cholesterol esters are covered by a layer of protein, cholesterol and phospholipid to form chylomicrons, which enter the lymphatic circulation

• most of the TG is formed by acylation of absorbed 2-monoglycerides at the SER, though, some is also formed from glycerophosphate from the glycolytic pathway
• the acylation of glycerophosphate and the formation of lipoproteins occurs in the RER
• CHO moeities are added to proteins in the golgi apparatus, and the conmplete chylomicrons are released by exocytosis
• the majority of absorption occurs in the proximal SI and on a normal diet less than 5% appears in the stools, most of this coming from cellular debris
• these processes are not fully mature at birth, and infants fail to absorb nearly 10-15% of their dietary fat

Absorption Of Cholesterol And Sterols

• cholesterol is readily absorbed if bile salts, FFA's and pancreatic juices are present
• absorption is said to be limited to the distal SI
• almost all of the absorbed cholesterol is incorporated into chylomicrons, which then enter the lymphatics
• closely related sterols of plant origin are poorly absorbed
• some of these reduce the absorption of cholesterol, probably by competing with cholesterol for esterification with FFA's

Water & Electrolytes

- ***Water, Sodium & Potassium***

• water balance in the GIT

1. Input: **9000 ml**
   - i. Ingested: 2000 ml
   - ii. Endogenous secretions: 7000 ml
     - salivary glands 1500
     - stomach 2500
     - bile 500
     - pancreatic 1500
     - intestinal 1000
2. Reabsorption: **8800 ml**
   - i. jejunum 5500
   - ii. ileum 2000
   - iii. colon 1300
3. Excretion in stools: **200 ml**

• thus, 98% of the fluid load is reabsorbed
• only small amount s of water move across the gastric mucosa, however, water moves freely across the SI in accordance with osmotic gradients
• Na^+ is actively transported from the lumen by pumps located in the baso-lateral cell membranes
• in the ileum and jejunum, this is facilitated by aldosterone
• luminal membrane transport is variably coupled to glucose, AA's or other substances
• the absorption of sodium is facilitated by the presence of the cotransported solutes
  → the use of NaCl & glucose solutions in diarrhoeal illnesses
• some E.coli and V.cholera produce a toxin which activates adenylate cyclase and increases cAMP
• this increases Clsecretion from the mucosa, and inhibits the function of the mucosal carrier for Na^+, reducing NaCl reabsorption
• however, the symport for glucose/Na^+ is unaffected
• duodenal contents may be hyper or hypo-osmotic, but the time the jejunum is reached the contents are iso-osmotic
• in the colon, Na^+ is actively pumped into the lumen and water follows

• for the majority, the movement of K^+ is by ***passive diffusion***
• the net movement being determined by the potential difference between the lumen and intestinal capillaries, leading to,

a.	jejunum	-5 mV	$[K^+]$ ~ 6 mmol/l
b.	ileum	-25 mV	$[K^+]$ ~ 13 mmol/l
c.	colon	-50 mV	$[K^+]$ ~ 30 mmol/l

• with the lumen negative and concentration being in the lumen
• thus, the loss of ileal of colonic fluids by diarrhoea leads to severe ***hypokalaemia***

Chloride & Bicarbonate

• in the ileum and colon, Clis actively reabsorbed in exchange for HCO_3^--
• this results in the intestinal contents becoming more alkaline

Vitamins & Minerals

Vitamins

• absorption of the water soluble vitamins is rapid and efficient
• the fat soluble vitamins, A, D, E, & K require normal fat absorption
• a deficiency of either bile salts or pancreatic juices will result in deficient absorption
• most are absorbed in the proximal SI, though, B_{12} is absorbed in the ileum along with intrinsic factor secreted by the stomach

Calcium

• absorption ranges from 30-80% and occurs mainly in the proximal SI
• some absorption is by passive diffusion, though, active transport is stimulated by Vit. D_3
• this stimulates the formation of Ca^{++} binding protein in the mucosal cells
• the exact relationship of these proteins to increased Ca^{++} absorption is unsettled
• this is under feedback control and GIT absorption is one of the main regulators of the plasma Ca^{++} levels
• absorption is also facilitated by lactose and protein
• it is inhibited by phosphates & oxalates, as these form insoluble salts

- ***Iron***

1. average daily losses
   i. men ~ 0.6 mg
   ii. women ~ 1.2 mg
      - losses for females vary considerably
2. average intake ~ 20 mg
      - but absorption is equal only to daily losses
3. absorption ~ 2-3%
4. normal plasma iron
   i. men ~ 130 µg/dl
   ii. women ~ 110 µg/dl

•
• more readily absorbed in the ***ferrous*** (Fe^{++}) state
• however, most dietary iron is in the ***ferric*** form (Fe^{+++})
• gastric secretions dissolve the iron and enable reduction to the ferrous state
• this is the reason iron deficiency anaemia follows gastrectomy
• ***ascorbic acid*** is another reducing agent in the diet which favors the conversion of the ferric the ferrous ion
• ***haem*** is also absorbed and the attached Fe^{++} is released by the mucosal cells
• absorption is an active process occurring mainly in the proximal SI
• ***mucosal transferrin*** binds iron in the lumen and transfers it across the brush border
• most of this is then transferred directly to the blood stream, but a significant amount is bound to ***apoferritin*** in the mucosal cells
• this iron is lost when the cells desquamate
• this protein combines with iron to form ***ferritin***
• each ferritin molecule may contain as many as 4500 molecules or iron, which exist in a micelle of ferric-hydroxyphosphate, contained within the protein
• ferritin molecules in lysosomal membranes may aggregate in deposits of > 50% iron

→ ***haemosiderin***

• approximate distribution in the body,

a. haemoglobin ~ 70%
b. myoglobin ~ 3%
c. ferretin ~ 27%

• ferritin is also found in the plasma, but most iron is bound to ***transferrin***
• this polypeptide has 2 binding sites and total saturation is usually ~ 35%

• in iron deficiency, the amount of ferritin is decreased and a greater fraction enters the plasma
• in overload, ferritin stores are large and absorption from the intestine is decreased → mucosal block

REGULATION OF GASTROINTESTINAL FUNCTION

Functional Anatomy

• there is some local variation, however, in general there are 3 layers of smooth muscle, 2 longitudinal & 1 circular
• the wall is lined by mucosa and , except in the case of the oesophagus, is covered by a serosa
• the serosa continues into the mesentry, which carries the nerves, blood vessels, and lymphatics

Innervation

• there are two major networks of nerve fibres which are intrinsic to the GIT, the,

a. myenteric plexus of Auerbach
   • between the outer lonitudinal and middle circular layers of muscle
b. submucous plexus of Meissner
   • between the middle circular layer and the mucosa

• these plexuses are interconnected and they contain nerves with processes which originate from receptors, either in the wall of the gut or the mucosa
• there are also an enormous number of interneurons
• the mucosal receptors include,

a. mechanoreceptors, sensitive to stretch
b. chemoreceptors, sensitive to changes in the contents of the lumen

• neurons innervate all of the muscular layers of the gut wall, other neurons innervate hormone secreting cells
• these constitute a complex enteric nervous system, which some authorities include as a third division of the autonomic system
• there are a total of ~ 106 neurons
• the secreted neurotransmitters include,

i. ACh
ii. enkephalins
iii. VIP
iv. CCK
v. NA
vi. gastrin releasing peptide GRP
vii. Substance P
viii. neurotensin

• coordinated motor activity of the gut occurs in total absence of extrinsic innervation
• extrinsic innervation is from both the PNS & SNS
• the preganglionic PNS fibres consist of ~ 2000 vagal efferents plus efferents from the sacral nerves
• they generally end on cholinergic nerves in either of the intrinsic systems
• the SNS fibres are postganglionic, but many of them end on postganglionic cholinergic neurons, where they inhibit ACh secretion
• others innervate blood vessels, producing vasoconstriction, while others end directly on intestinal smooth muscle

- ***Circulation***
    - see CVS notes on special circulations

Gastrointestinal Hormones

• there are a large number concerned with the regulation of GIT motility and secretion
• when given in large doses their functions frequently overlap, however, in physiological levels their actions appears discrete
• many of these fall into one of 2 families,

a.	gastrin family	- gastrin 34 - CCK 39
b.	secretin family	- secretin - GIP - glucagon - VIP - glicentin
c.	others	- motilin - substance P - somatostatin 14 - GRP

- ***Gastrin***

• produced by ***G cells*** of the lateral walls of the gastric antral mucosa
• receptors mediating gastrin responses to changes in the luminal contents are present in the microvilli
• like many other cells of the GIT secreting hormones, these contain amines related to NA & 5HT and are of neural crest origin $\rightarrow$ ***APUD cells***
• there is a second type of gastrin secreting cell found throughout the GIT, the TG cell
• this contains G_{34} but lacks G_{17}
• gastrin is also found in the pancreatic islets in foetal life and gastrin secreting tumors occur in the pancreas
• it is also found in the CNS, where it appears to act as a central neurotransmitter
• displays both macroheterogeneity & microheterogeneity

• the former referring to differences in peptide length, the later to differences in molecular structure due to differing AA's
• three main forms are found, G_{34}, G_{17}, & G_{14} gastrins
• all possess the same C-terminal tetrapeptide, which in itself has gastrin activity (~ 10% of G_{17})
• the G_{17} form is the principal agent in the regulation of gastric acid secretion
• the two smaller peptides have half lives of 2-3 mins, whereas the larger G_{34} up to 15 mins
• inactivation is primarily in the kidney and SI
• the physiological effects include,

a. gastric acid secretion
b. pepsin secretion
c. increased gastric motility
d. ? increased tone of the gastro-oesophageal sphincter
e. stimulates insulin & glucagon secretion after a protein meal

NB: ***atropine*** does not inhibit the response,
the transmitter probably being ***gastrin releasing peptide*** GRP

• also direct stimulation from the products of protein digestion, ie. AA's
• acid in the antrum inhibits secretion, providing a negative feedback loop

▪ ***Cholecystokinin***

• secreted by the cells of the upper SI
• results in both

a. increased secretion from the pancreas, and
b. contraction of the gallbladder

• like gastrin, it displays both macroheterogeneity & microheterogeneity
• prepro-CCK is processed into many fragments, from CCK_4 to CCK_{58}
• the major active fragments secreted by the duodenum & jejunum are probably CCK_8 & CCK_{12}
• the half life is ~ 5 mins, but little is known about its metabolism
• it is also found in cells in the ileum and colon, in parts of the CNS, and in nerves in many parts of the body
• other actions of the hormone include,

a. augmentation of the action of secretin
b. inhibits gastric emptying
c. increases the secretion of enterokinase
d. has a trophic effect on the pancreas
e. may enhance the motility of the SI and colon

• both CCK and gastrin stimulate the secretion of glucagon from the pancreas in response to a protein meal, and may be the "gut factor" responsible in vivo
• the action on the gallbladder may be mediated by cGMP

• secretion from the proximal GIT is stimulated by peptides, AA's and FFA's of more than 10 C length
• as bile increases digestion, a positive feedback loop exists, secretion being terminated by the passage of contents distally

- ***Secretin***

• first demonstrated by Bayliss and Starling in 1902, that the excitatory effect of duodenal stimulation on pancreatic secretion was due to a blood-borne factor
• subsequent research led to the discovery of secretin
• from this research, Starling introduced the term hormone to characterise chemical messengers
• secreted by cells located deep within the glands of the proximal SI
• the AA sequence is very similar to that of glucagon, VIP & GIP
• its half life is ~ 5 mins, little is known about its metabolism
• secretin increases the formation of bicarbonate by the duct cells of the pancreas and biliary tract
• thus, it causes a watery, alkaline pancreatic secretion
• its action is mediated by cAMP
• other effects include,

a. augments the action of CCK in stimulating pancreatic secretion of digestive enzymes
b. decreases gastric acid secretion
c. increases pyloric tone

• secretion of secretin is increased by the presence of the products of protein digestion and by acid in the proximal duodenum
• the increased alkaline secretion acts to neutralize the acid products entering the upper SI

- ***GIP***

• GIP is a 43 AA peptide found in the mucosa of the duodenum and jejunum
• its secretion is stimulated by the presence of glucose and fat
• it also stimulates the release of insulin, and evidence is accumulating that this is the GIT factor in physiological β-cell stimulation

- ***VIP***

• a 28 AA peptide found in many of the nerves of the GIT
• also found in the blood but the half life is only 2 mins
• it markedly stimulates intestinal secretion of water and electrolytes
• other actions include,

a. inhibition of gastric acid secretion
b. dilatation of peripheral blood vessels

• it is also found in neurons of the CNS, where it coexists with ACh
• in many tissues it potentiates the action of ACh

THE STOMACH

Functional Anatomy

- in the pyloric and cardiac regions of the stomach the glands secrete mucus
- in the body, including the fundus, the glands contain

a. parietal cells (oxyntic) → HCl & intrinsic factor

b. chief cells (zymogen, peptic) → pepsinogens

- these mix in the necks of the glands with mucus
- several of the glands open into a common chamber, a gastric pit
- the blood vessel and lymphatic supply is extensive
- the PNS innervation comes from the vagi
- the SNS innervation comes from the coeliac plexus

Gastric Secretion

- the average daily secretion of gastric juice ~ 2500 ml
- the hydrochloric acid secreted by the stomach has a number of functions,

a. kills many bacteria

b. aids protein digestion

c. provides the necessary pH for the activity of ***pepsin***

d. stimulates the flow of bile and pancreatic juices

- also contains mucus, which protects the mucosal lining against potential tissue damage
- this is secreted by cells in the necks of the glands and from the surface
- each glycoprotein molecule is made up of 4 subunits joined by disulphide bridges and the mucus forms a flexible gel that coats the mucosa
- the mucosa also secretes bicarbonate into the mucus, forming an unstirred layer with pH ~ 7.0
- the unstirred layer, plus the surface membranes of the mucosal cells and the tight junctions between them, form the mucosal bicarbonate barrier which is responsible for the protection of the stomach
- substances which tend to disrupt the barrier include,

a. ethanol

b. bile acids

c. aspirin and other NSAIDs

- prostaglandins stimulate mucus secretion, and their synthesis is inhibited by the NSAIDs
- the electrolyte content varies with the rate of acid secretion
- at low rates of secretion the [Na] is high, but as the rate of acid secretion increases the [Na] falls and [HCl] rises

Pepsinogen Secretion

• these are secreted by the chief cells as inactive precursors, the pepsinogens

Hcl Secretion

• transport of H^+ from the cytoplasm to the lumen of the canaliculi is by an active H^+-K^+-ATPase in the membrane of parietal cells
• there is evidence that the pump is synthesized in tubulovesicular structures at rest, and is then inserted into the membrane during stimulation of acid secretion
• it is difficult to obtain pure samples, however, secretion may be an isotonic solution of essentially pure HCL, with a pH as low as 0.87
• the cytoplasm is similar to other cells, being around pH ~ 7.0, the H^+ being pumped against an enormous concentration gradient
• the primary source of the secreted H^+ ion is from the ionization of water, being immediately extruded in exchange for K^+
• external K^+ ions are not required for secretion, K^+ readily diffusing across the membrane
• the presence of the H-K-pump is almost entirely limited to the parietal cells
• Cl^- is also actively transported into the gastric juice
• for each H^+ secreted an OH^- ion is neutralized by another H^+ supplied from the dissociation of carbonic acid
• the HCO_3formed is secreted into the interstitium in exchange for Cl^-
• the mucosa contains an abundance of carbonic anhydrase
• the stomach has a negative respiratory quotient $\rightarrow$ the venous blood has a lower PCO_2 than the arterial blood

• acid secretion is stimulated by,

a. H_2 histamine receptors $\rightarrow$ cAMP
b. M_1 muscarinic receptors $\rightarrow$ Ca^{++}
c. gastrin receptors $\rightarrow$ Ca^{++}

• the intracellular events interact, such that activation of one receptor type potentiates the response to another
• histamine comes from cells resembling mast cells, ACh from PNS endings and gastrin via the circulation

Gastric Motility & Emptying

• when food enters the stomach the organ expands = receptive relaxation
• followed by well developed peristaltic contractions, most marked in the distal half, occurring at ~ 3/min
• the pyloric sphincter has only limited function in the rate of emptying of the stomach
• this appears to be normal even if the pylorus is resected
• apparently the antrum, pylorus and upper duodenum function as a unit, coordinating the rate of emptying
• the peristaltic contractions of the stomach are coordinated by the gastric slow wave

• a wave of depolarization of smooth muscle cells spreads from the circular muscle of the fundus to the pylorus every 20 seconds
• this is also termed the basic electrical rhythm

▪ ***Regulation Of Gastric Emptying And Secretion***

• regulation is by both neural and humoral mechanisms
• the neural components are local autonomic reflexes, involving cholinergic neurons, plus impulses from the CNS via the vagus
• vagal stimulation results in,

a. release of gastrin-releasing peptide
b. release of gastrin
c. secretion of acid & pepsin, via ACh

• regulation of secretion of acid is usually divided into cephalic, gastric, and intestinal influences, though these overlap
• the cephalic influences are primarily mediated through the vagus,

a. food in the mouth
b. conditioned responses - smell, sight, thoughts
c. emotional responses

→ diencephalon and limbic systems

• the gastric influences are mediated by local reflex mechanisms and responses to gastrin,

a. food in the stomach
b. stretch and chemical stimuli, mainly AA's, on the mucosa
   → receptors entering Meissner's plexus
   → postganglionic parasympathetic neurons
   → parietal cells which secrete acid

• the reflex arc is totally within the wall of the stomach
• these neurons are the same as those which mediate the cephalic phases of secretion
• the products of protein digestion also bring about an increased secretion of gastrin

• the intestinal influences are mediated by reflex and hormonal feedback mechanisms from the mucosa of the small intestine
• fats, CHO and acid in the duodenum inhibit the secretion of gastric acid, gastric motility and pepsin secretion
• these effects are probably brought about by the secretion of GIP & secretin
• gastric acid secretion is increased following removal of large amounts of the small intestine, in a roughly proportional manner

- hypoglycaemia acts via the CNS and vagal efferents to stimulate acid and pepsin secretion
- the stimulation produced by insulin is the result of hypoglycaemia
- other stimulants include,

    a. caffeine

    b. alcohol

Regulation of Gastric Emptying and Secretion

- CHO leaves the stomach within a few hours
- protein rich foods leave more slowly, and emptying is slowest for fat rich meals
- the rate of emptying is determined by the osmolality of the contents reaching the duodenum
- hyperosmolality is sensed by duodenal osmoreceptors which initiate a decrease in the rate of emptying
- products of protein digestion and acid initiate a neurally mediated decrease in gastric motility, the enterogastric reflex
- this is also produced by distention of the duodenum

Peptic Ulcer

- related to a breakdown of the barrier which normally protects the mucosa from autodigestion
- in patients with duodenal and prepyloric ulcers, excessive acid secretion also plays a role
- however, this is not the case for other gastric ulcers
- there is a correlation between the levels of pepsinogen I, maximal acid secretion and the incidence of peptic ulceration
- resting gastrin levels do not appear to be elevated, but their gastrin responses to stimulation are greater than normal
- their parietal cells are also hyperresponsive to gastrin stimulation
- acid secretion is clearly involved in Zollinger-Ellison syndrome, where gastrinomas, usually in the pancreas, result in continued acid hypersecretion
- treatment is aimed at a reduction in the secretion of acid and enhancing the mucosal barrier

    1. ***gastric*** $\mathbf{H_2}$ receptors can be blocked with cimetidine or ***ranitidine***
    2. ***cholinergic*** $\mathbf{M_1}$ receptors can be blocked with atropine or the more specific antagonist ***pirenzipine***
    3. alternatively the H^+-K^+-ATP'ase can be inhibited by ***omperazole***

Other Functions of the Stomach

- HCL kills many of the ingested bacteria
- parietal cells secrete ***intrinsic factor***, necessary for the absorption of cyanocobalamin
- this cobalt containing vitamin is necessary for normal erythropoeisis, deficiency resulting in megaloblastic anaemia
- in pernicious anaemia, deficiency of intrinsic factor is due to idiopathic atrophy of the gastric mucosa
- intrinsic factor is a glycoprotein, MW = 45,000, the complex binding to specific receptors in the terminal ileum
- trypsin is required for this proces to be efficient, thus deficiency can also occur in pancreatic insufficiency
- in the blood stream, B_{12} is bound to transcobalamin II

THE EXOCRINE PANCREAS

Functional Anatomy

• compound alveolar gland resembling the salivary glands
• granules containing the digestive enzymes, zymogen granules, are formed in the cells and discharged by exocytosis
• the small duct radicals coalesce to form a single duct, of Wirsung, which usually joins the common bile duct at the ampulla of Vater
• the ampulla opens through the duodenal papilla, and is surrounded by the sphincter of Oddi
• there may be an accessory duct, of Santorini, entering more proximally

Composition of Secretion

• juice is highly alkaline, with a high [HCO_3^--]
• dialy secretion ~ 1500 ml
• bile and intestinal juices are also alkaline or neutral, and these three secretions neutralize duodenal contents, raising the pH to ~ 6.0-7.0
• the powerful proteolytic enzymes are secreted as inactive proenzymes
• trypsinogen is converted to trypsin by enterokinase / enteropeptidase, secreted by the duodenal mocosa
• secretion is increased by the hormone CCK
• trypsin then converts other inactive enzymes to their active forms,

a. chymotrypsinogens → chymotrypsin
b. proelastase → elastase
c. procarboxypeptidase → carboxypeptidase
d. trypsinogen → trypsin

*(d) forming a (+)'ve feedback

• deficiency of enterokinase leads to protein malnutrition
• the pancreas normally also contains a trypsin inhibitor, to protect againt autodigestion
• phospholipase A is activated by trypsin, splitting a fatty acid from lecithin, forming lysolecithin
• the later product damages cell membranes and its formation from lecithin in bile is involved in acute pancreatitis
• a small amount of α-amylase normall leaks into the circulation

■ ***Regulation Of Secretion***

• primarily under hormonal control
• secretin causes copious secretion of very alkaline pancreatic juice, relatively poor in enzyme precursors
• it acts on the epithelial cells of the small duct radicals, which secrete HCO_3^--, rather than the acinar cells
• as the rate of secretion increases, [Cl-] falls and [HCO_3^--] rises in a reciprocal fashion
• secretin also stimulates bile secretion

- CCK results in secretion of juice rich in proenzymes, acting on acinar cells with the release of zymogen granules
- vagal stimulation also causes a smaller but similar increase in secretion
- both act via an increase in intracellular [Ca^{++}]

LIVER & BILARY SYSTEM

Functional Anatomy

- organised into ***lobules***
- within which, blood flows from branches of the portal vein to a ***central vein***, through ***sinusoids*** lined with hepatic cells
- the sinusoidal capillaries have large fenestrations, allowing plasma close contact with the cells
- generally, there is only one layer of cells per sinusoid, creating a large area of contact
- blood from the ***hepatic artery*** also enters the sinusoids
- the central veins coalesce to form ***hepatic veins*** which drain to the IVC
- the average transit time for portal blood is ~ 8.5 s
- there are a large number of tissue macrophages, ***Kupffer cells***, which are anchored to the endothelium
- each hepatocyte is adjacent several ***bile canaliculi***, which coalesce to form the right and left ***hepatic ducts***
- these join outside the liver to form the ***common hepatic duct***
- the ***cystic duct*** drains the gallbladder to for the ***common bile duct***
- the mucous membranes of the cystic duct form the spiral vales of Heister

Functions of the Liver

- the liver is the largest gland in the body
- functions include,

1. formation of bile
2. CHO and intermediary metabolism
3. AA and ammonia metabolism
4. protein/glycoprotein synthesis and degradation
5. lipid metabolism - FFA's, TG and cholesterol
6. hormone synthesis & metabolism
7. detoxification of drugs and toxins
8. immune defence against agents entering the portal circulation

Compositon Of Bile

• bile is made up of,

a. bile pigments
b. bile salts
c. other substances - lecithin, FFA's, cholesterol
d. alkaline electrolyte solution - similar to pancreas

• average daily secretion ~ 500 ml
• some components are reabsorbed in the terminal ileum → enterohepatic circulation

• the bile pigments are the glucuronides of ***bilirubin*** & ***biliverdin***, and are responsible for the golden yellow color

• the bile salts are the sodium and potassium salts of ***bile acids*** conjugated to glycine or taurine
• the acids are based on the cyclopentanoperhydrophenanthrene nucleus
• there are two principal, or ***primary bile acids***, formed by the liver,

1. cholic acid
2. chenodeoxycholic acid

• 95% of these are reabsorbed in the terminal ileum, the remaining 5% entering the colon
• these are acted upon by bacteria forming the ***secondary bile acids***,

1. deoxycholic acid - most of this is absorbed
2. lithocholic acid - insoluble and mostly excreted in the stools ~ 99%

• average daily synthesis ~ 0.2-0.4 g
• the total bile salt pool ~ 3.5 g
• this recycles 6-8 times/day and 2 times/meal

• these salts have a number of important actions,

a. combine with lipids to form micelles → hydrotropic effect
b. with monoglycerides and phospholipids → emulsify fats
c. activate lipases in the SI

• in the absence of bile salts, ~ 25% of ingested fat appears in the feces, and there is severe malabsorption of the fat soluble vitamins

Bilirubin Metabolism & Excretion

- bilirubin is formed in the RES by the breakdown of ***haemoglobin***
- the ***globin*** moiety is split-off and returned for re-use
- the ***haem*** group converted to ***biliverdin*** and most of this is then converted to ***bilirubin***
- this is then transferred to the liver via the circulation, bound to plasma ***albumin***
- free bilirubin enters the hepatocytes where it is bound to cytoplasmic proteins, allowing continued diffusion
- conjugation to glucuronic acid is catalysed by ***glucuronyl transferase***, located primarily on the SER
- each bilirubin binds 2 glucuronide molecules, which are derived from uridine diphosphoglucuronic acid (UDPGA)
- this is then transported against a concentration gradient into the bile canaliculi
- some of this escapes into the bloodstream where it is excreted by the kidney
- the intestinal mucosa is relatively ***impermeable*** to bilirubin glucuronide
- however, it is permeable to unconjugated bilirubin and ***urobilinogens***, a series of colorless derivatives formed in the GIT by bacterial action
- consequently, there is some reabsorption, most of which enters the bile again but some of which is excreted in the urine

▪ *Jaundice*

- normal plasma bilirubin ~ 3.5-17.0 umol/l
- clinical jaundice is seen when the plasma bilirubin ~ 34 umol/l (2 mg/dl)
- ***hyperbilirubinaemia*** may result from,

1. excess production- haemolytic anaemia
2. decreased hepatic uptake
3. altered intracellular binding or conjugation
4. decreased secretion into the bile
5. intra, or extrahepatic biliary obstruction

NB: (a-d) → predominantly unconjugated bilirubinaemia
(e) → mixed bilirubinaemia