The Digestive System
GI TRACT

Introduction

In the next lectures and laboratory exercises we will discuss and examine the microscopic anatomy of the various parts of the digestive, or alimentary, system. Since this is a large and complex organ system, our coverage will not be total. We shall focus first on general principles and then proceed to a limited discussion of specifics, leaving it to you, by your readings, to round out the picture as time and inclination permit. You have examined the gastrointestinal tract in your cadavers and have learned the development of the system in the EMBRYOLOGY lecture. Functional correlates of the various structural features will be covered in detail in Physiology lectures.

It is fairly common to discuss the digestive system in three segments:
a) The oral cavity (including teeth and tongue) and the pharynx.
b) The digestive tube (or alimentary canal, or gastrointestinal tract) including esophagus, stomach, small intestine, and large intestine.
c) The accessory organs including salivary glands, pancreas, liver and gall bladder.

We shall not cover the elements of (a) in either lectures or labs. In the next two lectures and labs we shall consider the g.i. tract proper and then in subsequent lectures and lab we will study the accessory organs.

General Plan for the GI Tract:

Lecture 1: Organizational principles, esophagus and stomach
    Lab 1: Webslide examination of esophagus and stomach
Lecture 2: Small and large intestine
    Lab 2: Webslide examination of small and large intestine

The Alimentary Tube.

The digestive system (Figure 1) is a set of organs that function in the ingestion and digestion of food, the absorption of the useful products of that digestion, and the egestion of the waste products. The mouth and associated structures serve to select the food, separate it from the air, and, to a limited extent, process it mechanically and chemically. For the most part the business of the digestive system is carried out by the alimentary or gastrointestinal tube proper, a long (approximately 10 meters in humans), tortuous, fibromuscular pipeline which is structurally organized to transport food from mouth to anus, and in the process to disperse it mechanically, break it down chemically, and absorb the nutritive small molecules thus produced. As a rough approximation, the daily input to the system is about 500 grams of solid matter and 2.5 liters of water; after a processing time of 24-48 hours, the exiting residuum (faeces) consists of approximately 30 gm of solids and 100 ml of water. In these two lectures we shall discuss the structural features of the esophagus, stomach, small intestine, and large intestine as a basis for understanding their various functions.
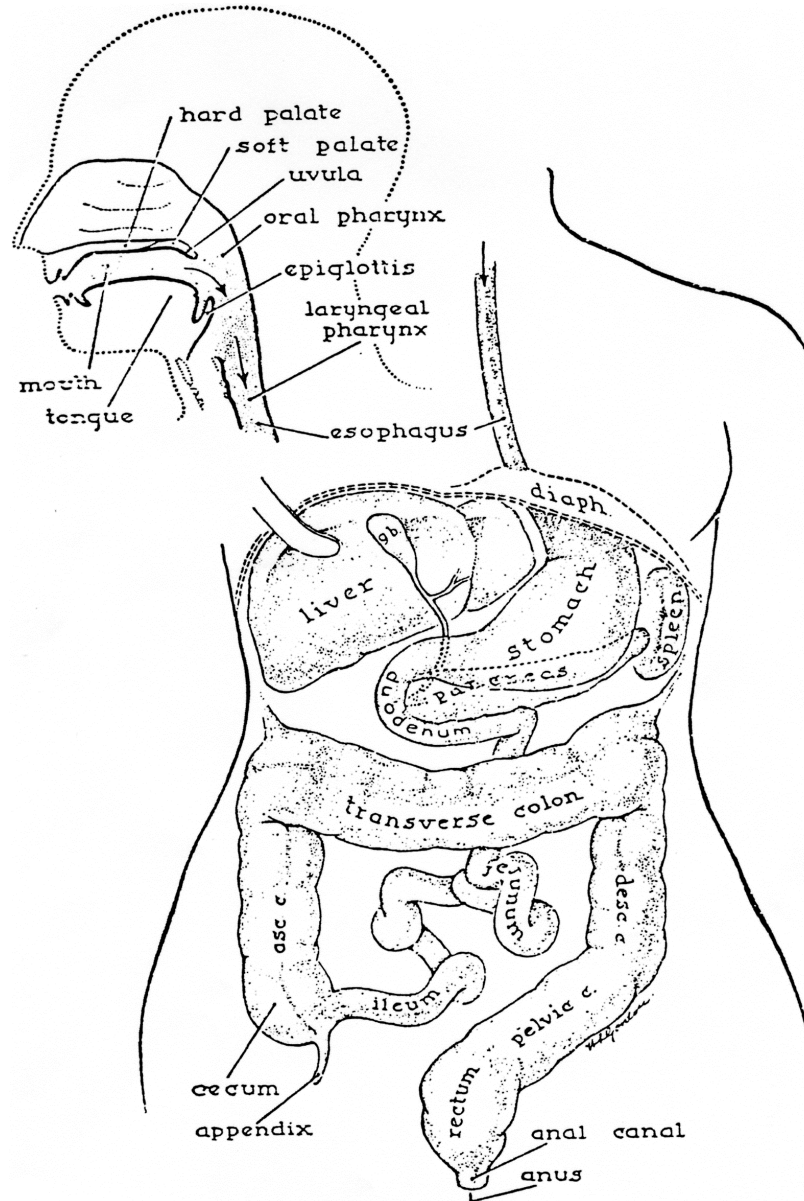
Figure 1. Organs of the digestive system

General Plan

In the wall of all parts of the alimentary tube four layers can be recognized: progressing outward from the lumen these are (1) the *mucosa*, (2) the *submucosa*, (3) the *muscularis externa*, and (4) the *serosa* or *adventitia* (Figure 2).

1. *Musosa:* Throughout the tube, the *mucosa* is itself divided into three layers.

a) *Epithelium:* The inner layer of the mucosa is an epithelium that varies from point to point in the tube, the structure directly related to function. Thus, in the esophagus, the epithelium serves a barrier or protective function and is *non-keratinized stratified squamous*; in the stomach the epithelium is secretory and is *simple columnar*; in the intestines, although there are secretory cells present, the epithelium functions mainly in absorption and one finds columnar cells whose

apical surfaces are folded (*microvilli*) to provide increased absorptive area. The microvilli represent but one level of epithelial folding serving to increase surface area. In the small intestine the epithelium as a whole is draped over conical or cylindrical projections of the underlying connective tissue, the combine projection being called a *villus*. Further, the entire mucosa may form similar "blankets" over peaks in the submucosa, in which case one speaks of *folds* or *rugae*. As a result of these multiple levels of folding the overall surface area of the alimentary canal is quite large: a value of 20-40 square meters has been estimated for the small intestine alone.

b) *Lamina propria:* Directly beneath the epithelium is a layer of loose, highly *cellular connective tissue* called the *lamina propria*. The lamina propria contains terminal vascular elements (small arteries, arterioles, veins, venules, and capillary plexuses) that not only nourish the overlying epithelium, but also carry off the products of digestion that are formed in the lumen and transported across the epithelial layer. Also important in the latter regard are *lymphatic vessels*, which are especially prominent in the small intestine. The lamina propria contains glands whose epithelia are continuous with the surface epithelium and which therefore release their secretory products to the lumen of the alimentary tube. Recalling the concept of the gut as a tube within a tube (Figure 1), and recognizing that the endodermally derived gut epithelium actually confronts the "external world", you should not be surprised to learn that the lamina propria contains many lymphocytes presumably involved in "second-line defense" against microbial invasion. In many places, the lamina propria contains distinctly lymphoid tissue, either as scattered patches, or organized into definite nodules.

c) *Muscularis mucosae:* The third layer of the mucosa is a narrow band of smooth muscle called the *muscularis mucosae*. Interspersed amongst the smooth muscle fibers are some elastic fibers. The muscularis mucosae receives sympathetic innervation and causes local movements and foldings of the mucosa. Although textbooks describe the muscularis mucosae as having two layers, an inner circular and an outer longitudinal one, you may have some (or lots of) difficulty discerning these layers in some your Webslides.

2. *Submucosa:* Immediately subjacent to the mucosa is the *submucosa*, a connective tissue domain which is denser and less cellular than the overlying lamina propria, and which, in some regions, has a fair amount of elastic fibers. The submucosa conveys the larger blood vessels and contains glands in parts of the esophagus and small intestine. At the base of the submucosa, between it and the underlying muscle layer (see below), is a plexus of nerve fibers (mostly unmyelinated), neuronal cell bodies, and supporting cells which constitute the *submucosal* or *Meissner's plexus*. The neuronal cell bodies include both ganglion cells of the parasympathetic division of the autonomic nervous system and numerous interneurons (also present in the myenteric plexus discussed below), which are part of a peripheral reflex system modulating both muscular and secretory activity. The postganglionic fibers of Meissner's plexus are primarily secretomotor to the glands of the submucosa and mucosa.
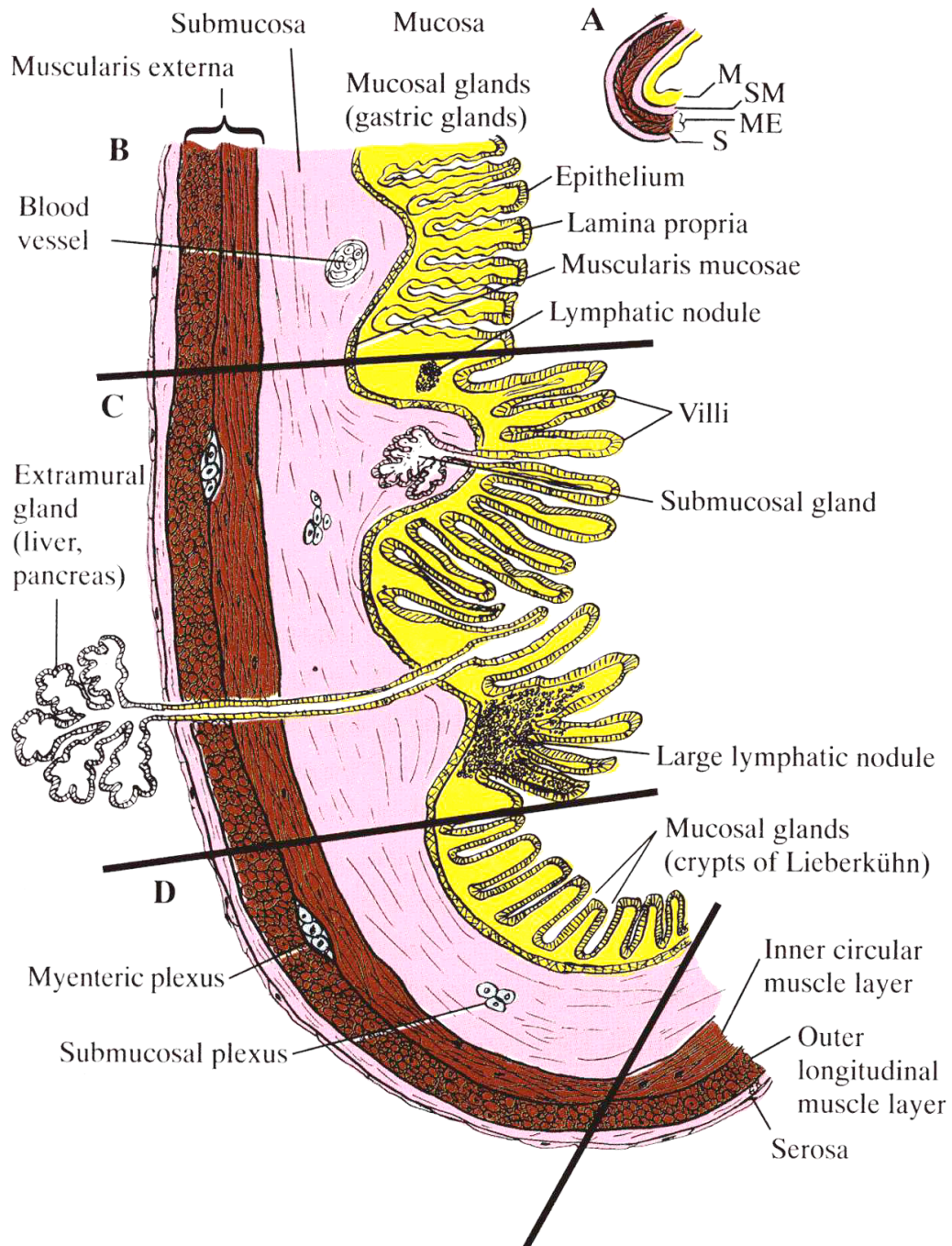
Figure 2. Schematic representation of the wall of the gastrointestinal tract (Ross et al, 1995. "*Histolology: A Text and Atlas*"). The small diagram (Panel **A**) shows the four layers of the GI tract: M = Mucosa, SM = Submucosa, ME = Muscularis externa, S = Serosa/Adventitia. The larger diagram is a higher magnification schematic with **B**, **C**, and **D** representing the stomach, small intestine, and large intestine, respectively.

3. _Muscularis externa:_ The next layer in the general plan of the digestive tube, immediately below the submucosa, is a robust layer of muscle called the _muscularis externa_. In most portions of the system the muscularis externa consists of two layers of _smooth muscle_: an inner layer in which the fibers run circumferentially around the lumen and an outer layer in which the fiber direction is predominantly longitudinal. In many portions of the tube the two layers of the muscularis externa are spirally oriented: the smooth muscle fibers in the outer layer run in a very slow spiral (large pitch), while those of the inner layer form a tight spiral (small pitch). Variations on this plan include the substitution of _striated muscle_ (upper esophagus), the presence of an extra layer (stomach), and the gathering of the outer layer into bundles (large intestine). Between the two layers of smooth muscle is a nerve plexus, the _myenteric_ or _Auerbach's plexus_, which includes prominent ganglion cells of the parasympathetic system. The postganglionic fibers of this plexus are locomotor to the muscularis externa. The muscles of the gut wall bring about the _peristaltic_ movement of food down the alimentary canal; in addition the muscles of the muscularis externa serves to break up food (_churning_ motions of stomach wall) and to mix the food with digestive enzymes (_segmentation_ and _pendular_ movements of intestines). The state of tonus of these muscle layers is important in determining the size of the lumen and the actual length (degree of folding) of the tube.

4. _Serosa or Adventita:_ The outermost layer of the alimentary tube varies in structure (and name) depending on the location. Most of the tube is covered by a _serosa,_ which consists of an inner layer of loose connective tissue and an outer layer of simple squamous epithelial cells called the _mesothelium_ of the visceral peritoneum. However, in some portions of the tube (e.g., esophagus), there is no mesothelium and the outer connective tissue domain, the _adventitia,_ grades directly into the surrounding connective tissue. The major blood vessels and nerve fibers with which you are familiar from gross anatomy traverse the serosa or adventitia en route to the inner layers of the gut wall.

Regional Structural Variations

We shall now consider some of the specific variations found in the different regions of the GI tract, commenting briefly on the functional implications. This discussion is most conveniently presented in terms of the progress of a meal through the human digestive system. The digestive system goes into action even before food enters the mouth, when the smell and sight of food trigger (via involuntary reflexes) release of the secretory products of salivary glands into the oral cavity. Food is moistened and coated with mucus in the mouth (easing its passage down the pharynx, etc.), dispersed mechanically by the action of the teeth, and exposed, albeit briefly, to the salivary amylase, ptyalin. Although the ingested food is not significantly digested in the oral cavity, the traces of small molecules that are washed out of it (such as sugars, salt) stimulate the taste buds of the tongue and leading to further secretion into the oral cavity as well as to the onset of gastric secretion (cephalic phase - see below). A portion of the chewed, moistened food is then transferred to the pharynx by the tongue, and swallowed. The initial phase (movement by tongue) of deglutition or swallowing is under voluntary control, but the rest of the transfer of food through the pharynx and beyond is a reflex act; until the food (or food remnants) reaches the anal sphincter its movements are under involuntary control.

Esophagus

The esophagus (Figure 3) is a fibromuscular tube approximately 25 cm long in adults that functions to convey food from the laryngeal pharynx to the cardiac region of the stomach. No digestive action occurs in this region of the alimentary tube and the variations on the general structural plan reflect this. The mucosal epithelium is of the *non-keratinized stratified squamous* variety, as you might expect from consideration of the rather rapid (about 2 seconds) passage of food (frequently rough) down the esophagus. Sometimes in mammals with more abrasive diets (ruminants, some rodents, herbivorous primates) the esophageal epithelium is keratinized. However, in humans nuclei are detectable in cells of the most apical layer. The surface of the epithelium is fairly smooth, but the lamina propria contains numerous small papillae and the basal layer of the epithelium follows the trough-and-peak architecture of the underlying connective tissue. The *submucosa* contains tubulo-acinar *mucous glands* (right hand side of Figure 3). The ducts of these *esophageal* glands pierce the muscularis mucosae and traverse the lamina propria, conveying the mucous secretion to the esophageal lumen, thus aiding in the lubrication of the passage of the food *bolus*, which was begun in the mouth.
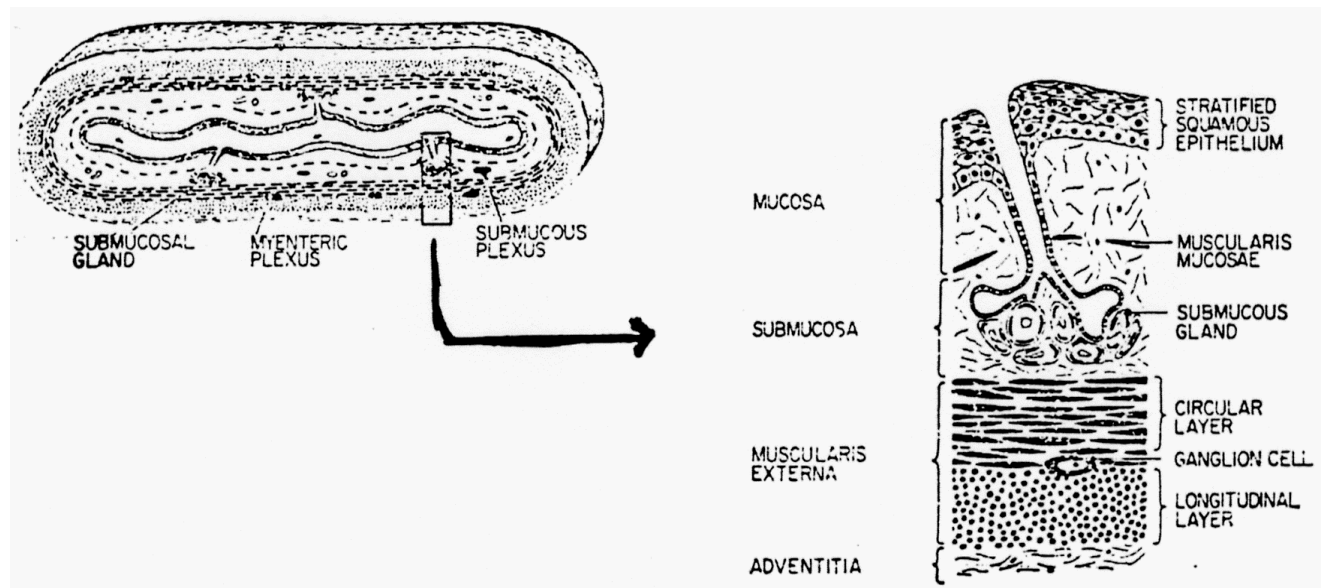

Figure 3. Schematic drawings at low power (left) and higher power (right) of the esophagus.

The muscularis externa consists of two muscle layers that are regionally specialized in humans. In the *upper third* of the esophagus only *skeletal muscle* is found, while in the lower third only *smooth muscle* fibers are present. In between there is a general transition (intermingling of fiber types) from striated to smooth muscle; most texts agree that little skeletal muscle is detectable beyond the half-way point. Except for the initiating movement of the tongue, the act of deglutition is a reflex act. The skeletal muscle fibers of the upper and middle esophagus are innervated by special branches of the glossopharyngeal and the vagus: these branches are not autonomic in the sense that they send efferent fibers directly to motor end plates. The vagal innervation of the smooth muscle of the distal esophagus is more typically autonomic in that preganglionic fibers synapse with ganglion cells in Auerbach's plexus and postganglionic fibers innervate the smooth muscle. The muscularis externa of the distal esophagus is specialized at the region of the junction between esophagus and stomach to form

the so-called lower esophageal sphincter (LES), which prevents reflex of gastric juices into the esophagus. As an anatomical entity the LES is less distinct than the pyloric sphincter (see below). Some authors report a slight thickening of the inner (circular) muscular layer at this point, whereas others claim that a flap or fold of mucosa hangs down to block or partially block the lumen. Apparently, the muscle cells in this region are specifically innervated in some poorly understood fashion. Furthermore, the stomach hormone *gastrin* (see below) affects the muscle cells of the LES.

Except where it closely approaches the pleura, the cervical and thoracic esophagus is surrounded by *adventitia*; the small portion (about 2 cm) within the abdominal cavity and connecting with the stomach is covered by a serosa (peritoneum).

Stomach

The food bolus, having traversed the esophagus, reaches the stomach (Figure 4), a fibromuscular bag whose functions include storage as well as mechanical and chemical processing of the food. The stomach can be divided into four anatomical regions (Figure 4A): the *cardiac* region is adjacent to the esophagus, the *fundic* region is above the level of a horizontal line drawn through the esophageal orifice, the *corpus* (body) comprises the main central region, and the *pylorus* (*pyloric antrum*) is the region adjacent to the small intestine.

At the *gastroesophageal* junction between the esophagus and the cardiac stomach there is a striking and abrupt transition of the surface epithelium from stratified squamous in the esophagus to *simple columnar* in the stomach. The stomach has a storage capacity of 1/2 to 1 liter, the exact reservoir size depending on the degree of stretching of the convoluted walls. These convolutions are called *rugae*, which are the macroscopic folds observed in dissection of the stomach. The rugae, which run predominantly longitudinally, are upthrusting folds of the submucosa upon which is draped the entire mucosa. These rugae are almost completely flattened out in the distended (full) stomach.

Examination of the stomach mucosa with the Virtual Microscope at fairly low magnification reveals that the surface epithelium is not smooth, but is folded into *mucosal glands* (illustrated in Figures 2B, 4B, 4C, and 4D). The folding pattern of these glands is unique to the stomach and therefore <u>key to identifying</u> the stomach in Virtual Microscopy sections. Specifically, the stomach mucosal glands can be divided into two distinctive regions: *gastric pits* and *gastric glands*. The fairly wide *gastric pits* extend from the lumen into the lamina propria, about 1/4 to 1/3 of the way to the muscularis mucosae. At the base of the wide pits the epithelium turns into *gastric glands,* which are narrower in diameter than the pits and extend down to the muscularis mucosae (Figures 4B and C).

Simple columnar epithelium lines the surface of the pits and glands throughout the stomach (Figure 4D). All of the surface cells in the pits produce a mucous secretion and are therefore referred to as *mucous surface cells* (Figure 4D). These rectangular mucous surface cells are different from the goblet cells seen in the intestinal epithelium, which are distended apically (hence the term *goblet*) by their secretory product. The mucous surface cells differ in appearance from the *mucous neck cells* of the glands in the lamina propria, because there is often less secretory product visible in the cytoplasms of the neck cells (Figure 4D). However, the types of epithelial cells in the glands vary, depending on the region of stomach, as described in the next section.
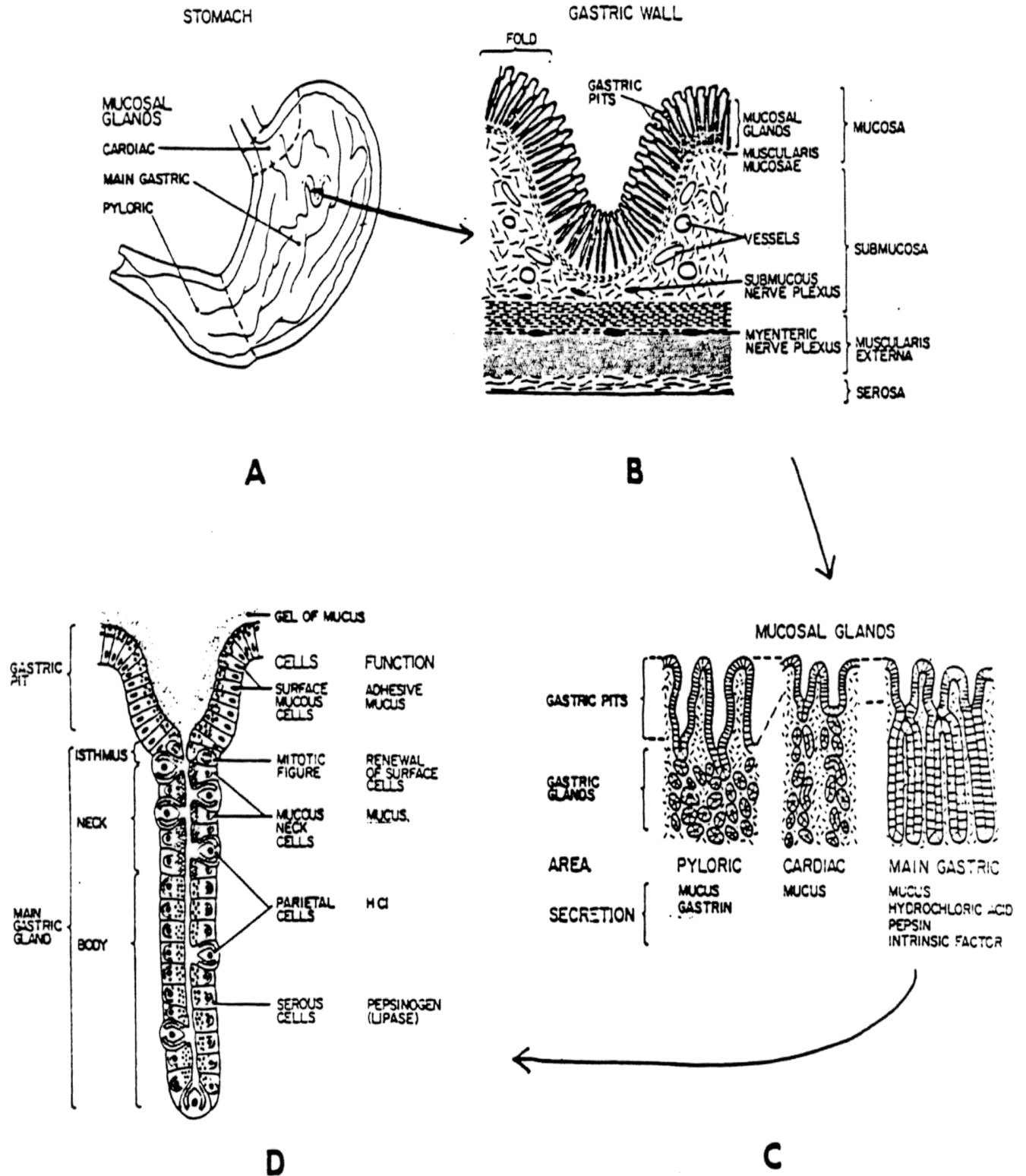
Figure 4. Progressing clockwise from A to D are schematic representations at increasing magnifications of the stomach, stomach wall, mucosal glands, and a gastric (fundic) gland.

Although all gastric glands are continuous with the bases of the gastric pits, these glands differ in shape and cell types from region to region (Figure 4C). The bulk of the gastric mucosa contains the so-called *main gastric (fundic) glands*, which are distributed throughout the corpus and fundic regions of the stomach and cover about 70-80% of the stomach's surface. These main gastric glands are tubular glands that run perpendicular to the lumenal surface, extending from the base of the gastric pits to the muscularis mucosae--they are 2-3 times as deep as the pits. As shown in Figure 4D, in these *main gastric glands* the epithelium of the isthmus, neck and base contains four types of cells, not evenly distributed:

(1) *Mucous neck cells*, found primarily in the neck (top) of the gland, are thought to produce a slightly different secretion from the mucous surface cells. They probably also release *A* and *B blood-group substances* which are thought important in the protection of the mucosal surface, since type 0 individuals are more prone to *ulcers*.

(2) *Parietal cells (oxyntic cells)* secrete HCl and are thus responsible for creating the acid milieu of the stomach. They are large rounded cells found in the neck and isthmus, and, to a smaller extent, in the base of the gland. They are characterized by an elaborate intracellular system of membranous channels or canaliculi and by a profusion of mitochondria. Parietal cells execute a complex series of ion pumping reactions, the net result of which seems to be the release to the interstitial space (hence endocrine-like secretion) of $NaHCO_3$ and to the glandular lumen (hence exocrine) of HCl. They also are probably the source of "intrinsic factor", a mucoprotein required for the efficient absorption (in the intestines) of vitamin B-12.

(3) *Chief (serous) cells* are found in the base of the gland. Because they produce pepsinogen, a precursor to pepsin, these are often called zymogenic cells. However, in your Webslides their secretory granules are not as obvious as those of pancreatic acinar cells. Occasionally chief cell granules appear somewhat pale, suggesting that the cells are intermediate in the serous-mucous spectrum. The chief cells also produce rennin (the enzyme present in infants which curdles milk) and probably other enzymes, among them a lipase.

(4) Endocrine (paracrine) cells (originally called argentaffin or argyophilic cells by histologists based on staining reactions) are recognized as being oriented in the opposite direction from mucous, parietal, and chief cells. That is, because endocrine cells secrete into the underlying connective tissue (and not into the lumen of the gland), the nucleus is often located near the apex of the cell and secretion granules are situated between the nucleus and the basal lamina. The apices of these cells may or may not be in continuity with the glandular lumen. There are really two types of cells in the GI tract that secrete peptides into the underlying CT, *endocrine cells* and *paracrine cells*. Endocrine cells secrete hormones into the blood stream, whereas paracrine cells secrete substances that act on neighboring cells. That is, paracrine secretions do not have to enter the blood stream, but rather diffuse through the connective tissue to act locally. An example of a paracrine substance secreted by cells in the GI tract is somatostatin, which inhibits certain endocrine cells in the mucosa.

The mucosal glands of the *cardiac* and *pyloric* regions of the stomach are different from these main gastric glands (Figure 4C). The *cardiac glands*, which only occur over an area of about 10-15 cm^2 centered on the gastro-esophageal junction and can sometimes be found in the lamina propria of the distal esophagus, are shorter and more branched than the fundic glands. The cardiac glands contain mostly mucous cells, with few chief cells and virtually no parietal or

endocrine cells. Over the approximately 15% of the stomach mucosa centered on the *pyloric sphincter* are *pyloric glands*, whose gastric pits are deeper and whose glands are often more coiled and branching than the main gastric glands. Although in humans the *pyloric glands* contain a few parietal cells, there are essentially <u>no</u> chief cells, the main type being a cell with a rather pale, apparently mucous-containing cytoplasm. These pyloric glands do contain endocrine cells, which produce the polypeptide hormone *gastrin*. Gastrin is released into the circulation when food enters the stomach and stimulates release of the acid secretions of the main gastric gland--a stimulation that is counteracted when the acidity of the stomach contents gets too high. As previously noted, gastrin also affects the muscularis in the LES.

Because the stomach mucosa is packed with glandular epithelium, the *lamina propria* is not obvious as a continuous layer, being found essentially as thin strands between the glands. The muscularis mucosae is prominent in the stomach as a distinct layer delimiting the bases of the mucosal glands. Elastic fibers of the submucosa account for the stretch ability of these folds and thus the dispensability of the stomach. The Meissner's plexus of the stomach submucosa is fairly prominent, the fibers being secretomotor to the mucosal glands.

The muscularis externa is quite robust in the stomach. In the cardiac region there is an additional, *innermost*, layer of obliquely oriented smooth muscle fibers, which is scanty elsewhere in the stomach and often difficult to see in a given histological preparation. In the stomach, the middle layer of circularly oriented smooth muscle is thickened at the juncture between the pyloric stomach and the small intestine (duodenum) forming the *pyloric sphincter*. A true *serosa* surrounds all regions of the stomach.

Food, having traversed the esophagus rapidly, spends a few minutes to a few hours within the stomach. During this interval, the food is blended with the copious (up to 1.5 liters/day) acid secretions of the gastric mucosa, thorough mixing being assured by the churning and peristaltic actions of the muscularis externa. The most vigorous mixing occurs in the pyloric antrum and the longitudinally oriented rugae tend to funnel the food, repeatedly displaced upward by the churning of the muscularis, back down to the pylorus. Exposure to the acid mixture of gastric enzymes converts the fairly solid ingesta into a creamy semi-solid mass called *chyme*, which, in small portions, is passed through the pyloric sphincter to the duodenum. While food is thus at least partially digested in the stomach, little absorption takes place there, with the exceptions of water and alcohol. Thus, the stomach functions as a preprocessing plant for the small intestine. Although these preprocessing operations are highly useful, they are not indispensable, since persons with total gastrectomy seem to function quite well.

The highly acid milieu of the stomach (pH approximately 1.0 to 1.5) is suitable for the actions of the gastric enzymes and also has a bacteriocidal or bacteriostatic effect. This acidity, which is entirely due to the actions of the parietal cells, poses severe problems for the gastric mucosa--problems that appear to have been solved by extensive overproduction of mucous material which coats and protects the epithelium. Nevertheless, the wear and tear on the epithelium of the gastric mucosa is significant and there is extensive cell turnover. The mucous surface cells seem to be replenished by virtue of mitotic activity in the isthmus regions of the fundic glands, but the turnover of parietal and chief cells is less well understood. Exactly how the stomach normally manages the trick of not totally digesting itself is not clear and the frequency of peptic ulcers of the gastric mucosa is a testimony to the fact that the mechanism isn't perfect. With regard to the recognized connection between tension (or anxiety) and ulcers, you should realize that the control of gastric secretion (which can range from a basal rate of

about 10 ml/hr to more than 100 ml/hr) involves an initial cephalic phase (psychic factors including emotional state, sight and smell of food, etc.), a second gastric phase (ingested food directly or indirectly, via gastrin, induces secretion), and a third or intestinal phase (in which products of the intestinal mucosa enter the circulatory system and further stimulate gastric secretion).

Small Intestine

The partially digested food (chyme) passes through the pyloric sphincter and into the small intestine (Figure 5). This is a tube some 7 meters long in humans consisting of, in proximo-distal order, the *duodenum* (about 25 cm), the *jejunum* (2.5 to 3 meters) and the *ileum* (about 4 meters). In the small intestine the degradative phase of digestion is essentially completed and most absorption of nutrients occurs. Accordingly the mucosa is highly specialized, primarily for absorption, but also for secretion. To facilitate absorption, the intestinal wall has a very large surface area due to the folding of the mucosal elements at three levels;

(1) The entire mucosa is thrown into deep folds called *plicae circulares*, which run circumferentially or spirally (upper right hand panel of Figure 5A). Plicae begin in the distal duodenum, reach maximal size in the jejunum, begin to diminish in the ileum, and are nearly absent in the distal ileum. The large plicae of the jejunum may project up to 1 cm into the intestinal lumen. Unlike the longitudinal folds or rugae of the stomach, the plicae of the intestine are not flattened out when the lumen is full.

(2) Superimposed upon the plicae, the epithelium and lamina propria (but not the muscularis mucosae) contain smaller folds called *villi* and *crypts (glands)*. Villi (unique to the small intestine in the GI tract) are projections into the lumen of up to 1 mm in length that cover the intestinal wall giving it the velvety texture observed in gross dissection (Figure 5A and B). It is said that the villi of the duodenum are broad and leaf-like, those of the jejunum are tall and tongue-like, and that those of the ileum are shorter and more finger-like. However, such distinctions may not be possible with your slide materials as there are often quite wide variations from this "general" plan and there is a continuous gradation from one to the other. Villi are not static entities; their surface epithelium is being continuously renewed and the villi are in constant, functionally significant, motion. In between the villi are places where epithelium extends down into the mucosa in glands or *intestinal crypts* (*crypts of Lieberkuhn)*.

(3) Some intestinal epithelial cells contain closely packed *microvilli* (*striated border*) at their apical surfaces. Microvilli are about 0.5 to 2 μm in length, approximately 0.1 μm in diameter, and since the number per cell may be several thousand, the surface membranes of these absorptive cells (enterocytes) extend over very large areas.
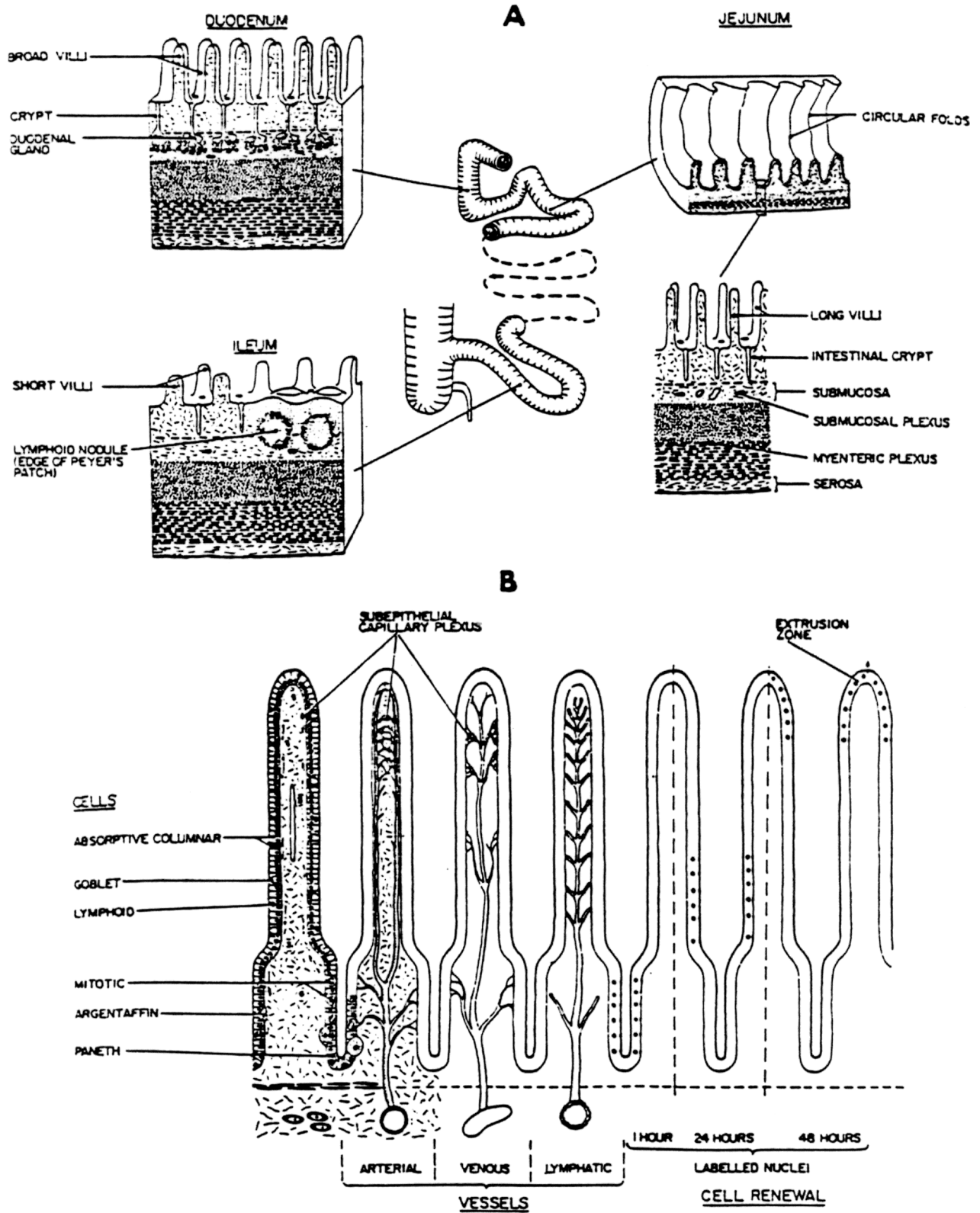
Figure 5. The small intestine: (**A**) Schematic diagram showing circular folds (plicae), villi, and crypts; (**B**) Some details of the structure of intestinal villi and crypts.

Throughout the small intestine the mucosal epithelium is *simple columnar*, containing the following cell types.

(1)   A*bsorptive cells (enterocytes)* are tall columnar cells with a microvillous border reflecting their role in absorption. They are found primarily on the villi, but can also extend into the crypts.

(2)   G*oblet cells* are mucous-secreting cells whose product serves to coat the surface epithelium, in some way protecting it from digestive juices without preventing absorption of the small molecule nutrients produced by digestion.   Goblet cells are found both in villi and in the glands.

(3)   *Paneth cells* are serous exocrine cells (basal nucleus in basophilic cytoplasm, apical secretory granules next to the granular lumen) that secrete lysozyme, an enzyme that digests the cell walls of certain bacteria. It therefore thought that Paneth cells help to control the bacterial population in the intestine. These Paneth cells are unique to the small intestine and found at the base of the crypts, just above the muscularis mucosae.

(4)   Endocrine cells are found in the crypts and are very important in producing polypeptide hormones such as gastric inhibitory polypeptide (GIP), cholecystokinin (CCK), and secretin. As detailed in the physiology lectures, these hormones can affect cells in the GI tract as well as in the associated GI glands, such as the pancreas.

(5)   *Immature cells* in the crypts are found near the base of the crypts. Since this region of the crypts is one of intense mitotic activity, these low columnar cells are thought to be precursors of the absorptive cells covering the villi. The villus epithelium is turning over rather rapidly; various experiments indicate that in man the surface epithelial cells are completely replaced every few days. New cells move up along the surface of the villi and eventually, having "grown old", are shed at the tips of the villi, their remains being excreted with the faeces. It is postulated that the slips of smooth muscle in the lamina propria core of the villus (which run perpendicularly from the underlying muscularis mucosae and appear to attach to the basement lamina beneath the tip of the villus) may bring about the dislocation of old cells from the villus tip by virtue of their periodic contractions (see below).

(6)   *Microfold (M) cells* have folds (rather than microvilli) on their apical surfaces. M cells take up macromolecules from the gut lumen and transport these antigens to the intercellular space near the lymphocytes. The lymphocytes in these various locations are functioning in a "second-line defense" capacity against microbial "invaders". Microfold cells are not easily detected in most sections, but can be detected immediately above the lymph nodules in the ileum in your Webslide #0096.

The cores of the villi consist of a lamina propria, which is a highly cellular loose connective tissue. The vasculature of this region is particularly rich, the capillary network serving to supply the overlying epithelium, as well as carry off the final products of digestion. In addition, large lymphatic vessels are found which function in the transport away from the gut of the products of *fat digestion*; after a meal, the filling of these lymphatics with large fat droplets, *chylomicrons*, gives them the milky appearance from which the term *lacteal* derives. The lamina propria of the intestinal mucosa also contains numerous reticular fibers and is, in many ways, lymphoid in character: isolated patches of lymphoid tissue are found throughout the mucosa of the small intestine and lymph nodules are fairly common. Lymphocytes are often found associated with microfold cells.

The muscularis mucosae does not protrude into the cores of the villi; however, small slips of smooth muscle are found in the lamina propria of the villi running perpendicularly to the muscularis mucosae. Observations on "living" intestinal mucosa have revealed that the villi wave about and contract (by about l/2 their length) several times per minute. It seems reasonable to assume the smooth muscle slips cause these rhythmic shortenings which, in addition to forcing blood and lymph out of the vessels of the villi (and into the drainage vessels of the submucosa), may aid in the tip dislocation of "old" epithelial cells.

The submucosa is unremarkable except in two regions (the *duodenum* and *ileum*) and these regional difference can help one distinguish these regions of the small intestine. The *glands of Brunner* are found in the *duodenum*. These are branched and coiled tubular glands, the ducts of which penetrate the muscularis mucosae and connect with the bases of the crypts of Lieberkuhn. The cells of the secreting portions of Brunner's glands are pale staining, but do contain secretory granules. They are thought to be intermediate between mucous and serous types, but their products are not well defined. It is known that the secretion from these glands is slightly viscous and distinctly alkaline, and is important in protecting the intestinal epithelium and (along with bile and the pancreatic secretions) in helping to neutralize the acid chyme entering the duodenum. The importance of this "neutralizing" action should not be under-estimated: even so, the proximal duodenum is quite prone to *peptic ulceration*. Brunner's glands are primarily localized in the duodenal submucosa, but can occasionally be found in the distal pylorus and/or the proximal jejunum.

In the *ileum* aggregates of many lymph nodules are common, and can be so large as to protrude into the submucosa and distort the contours of the tube so as to be visible on gross inspection. Such large masses of lymph nodules are referred to as *Peyer's patches*. It should be remembered that isolated lymph nodules are found throughout the G.I. tract, and it is these extensive aggregates of nodules that distinguish the ileum.

The muscularis externa of the small intestine is typical of the general plan and shows the myenteric plexus particularly well. Except for the portion of the duodenum, which is retroperitoneal, the small intestine is covered by a true serosa, which is continuous with the supporting mesentery.

In considering what happens to food in the lumen of the small intestine, you must remember that, in addition to the secretory products of the intestinal mucosa and submucosa, the small intestine also contains the substances released from the liver and pancreas (as well as from the storage reservoir--the gall bladder) and conveyed to the duodenum via a combined duct which opens on the *duodenal papilla* roughly 8 cm below the pyloric sphincter. We will discuss the liver and gall bladder later and you will learn that the pancreatic secretion is alkaline and contains various proteases, as well as enzymes which degrade fats and carbohydrates; the bile produced by the liver is also slightly alkaline and contains bile salts which help emulsify fat thus facilitating its digestion and absorption. Thus, the acid enzyme, which enters the small intestine is neutralized and made slightly alkaline, then degraded to the small molecule stage by a mixture of enzymes. Mucus secreted by the goblet cells of the surface epithelium, as well as by the crypts and Brunner's glands, helps protect the mucosa from digestion and the columnar absorptive cells take up the small molecule products of digestion for processing and subsequent release to vascular and/or lymphatic vessels.

It is important to stress the secretory role of the columnar enterocytes, with their microvillous border, in the processing of food in the intestine. These intestinal cells produce a series of hydrolytic enzymes including the disaccharidases and the trypsinogen-activating enzyme enterokinase. While a significant percentage of the activity (10-20%) of these enzymes is present in the intestinal lumen, most of the activity is associated with the *glycocalyx*, the glycoprotein coating of the microvilli. Thus these enzymes are secreted by the cells but retained as an extracellular coat involved in the absorptive processes outlined below. The small amounts of activities present in the GI lumen are thought to represent the remains of worn out surface cells shed at the tips of the villi. These cells carry out a complex series of secretory and absorptive steps, which can be outlined as follows:

(1) *Carbohydrate* molecules are apparently degraded to disaccharides in the GI lumen and are then hydrolyzed to monosaccharides by the enzymes of the microvillous border. The monosaccharides thus created are then actively transported into the cells perhaps coupled to an ion pumping mechanism. Transport out of the cells to the interstitial spaces probably occurs via passive diffusion. When the disaccharidases are absent from the microvillous border, disaccharides are left in the lumen and are fermented by bacteria in the large intestine, thus giving rise to diarrhea.

(2) *Peptide* hydrolysis may occur at the brush border, whereas the processing of *proteins* to amino acids appears for the most part to proceed in the GI lumen. Movement of the amino acids then seems to follow by mechanisms similar to those involved in sugar transport.

(3) *Fats* are degraded to free fatty acids, mono- and diglycerides by enzymes free in the GI lumen. These digestion products (emulsified with bile salts) then diffuse freely (are not pinocytosed or actively transported) across the apical plasma membrane of the columnar cells. Once inside, these compounds are taken up by the smooth ER and resynthesized into triglycerides. Specific protein molecules supplied by the rough ER coat the triglyeride droplets, forming *chylomicrons* that are secreted into the lateral spaces between cells and then move into the *lacteals*.

(4) *Ions* move across the *epithelium* either by diffusion or coupled to the transport of sugar and amino acids. A sodium pump in the lateral membranes pumps sodium out into the interstitial space.

(5) *Water* follows ion flow in an essentially passive manner satisfying osmotic balances. Some ions are not easily absorbed and cause the retention of water in the intestines: this explains, for example, the purgative action of Epsom salts.

(6) *Alcohol* diffuses freely across the membranes of the columnar epithelial cells.

The breakdown products of *proteins, carbohydrates,* and *nucleic acids* enter the mucosal blood *capillary plexuses* and are routed via the *portal circulation* to the liver. However, *fat* (in the form of chylomicrons) travels via the *lacteals* into *lymphatic vessels* and thence into *systemic circulation*.

Finally, it should be pointed out that not all of the columnar cells carry out all of these processes: this fact (and others) helps account for the finding that the absorption of various substances tends to be somewhat regional. Most absorption occurs in the jejunum, but the ileum is also active and the absorption of vitamin B-12 occurs primarily in the distal ileum. Absorption of water and electrolytes begun in the small intestine is completed by the large intestine.

Large Intestine

Food leaves the small intestine via the ileocaecal valve or sphincter and enters the large intestine, a tube about 1.5 meters long consisting of the *cecum*, *colon*, *rectum* and *anal canal* (Figure 1). Although the large intestine produces no digestive enzymes, some degradative action continues in the watery chyme that enters from the small intestine. This is due both to residual activity of the enzymes of the small intestinal lumen, as well as the putrefactive action of bacteria that populate the large intestine. For the most part, however, the large intestine is involved in the removal of fluid from the watery food mass in the upper portion and the temporary storage of the semi-solid waste material (faeces) thus produced in the lower portion. Food passes through the small intestine and proximal large intestine over a period of three to four hours; the faecal contents may remain in the distal large intestine anywhere from a few hours to one or more days.

The mucosa of the large intestine contains <u>no</u> villi. Instead, the mucosal layer shows a rather smooth surface marked by deep crypts (Figure 6A), the *glands of Lieberkuhn*. The crypts are <u>straight tubules</u> that, because the mucosa is somewhat thicker than that of the small intestine, are longer than those of the duodenum, jejunum, or ileum. Furthermore, the lumens of the crypts of the large intestine are usually patent and quite obvious. The epithelium of these glands is simple columnar, containing similar cells types as the small intestine: (1) *absorptive cells* with short microvilli, (2) *goblet cells*, (3) *immature cells*, and (4) a few *endocrine cells*. However, there are <u>no</u> Paneth cells. Turnover of the mucosal epithelium is rapid with mitosis occurring mostly in the middle third of the crypts and extrusion of older cells taking place on the surface midway between pits.

Over most of the large intestine the *lamina propria* is similar to that of the small intestine with abundant lymphoid tissue often present as nodules extending into the submucosa. Lymph nodules are quite common in the *appendix*, a blind-ended 2 to 10 cm long tubular structure extending from the cecum (see Figure 1). Because the appendix is blind-ended, intestinal contents can be trapped here, sometimes leading to severe inflammation and infection (appendicitis). The *muscularis mucosae* is present in the *cecum*, *appendix*, *colon*, and *rectum*, but <u>disappears</u> in the *anal canal*, where the mucosa and submucosa are therefore less well demarcated.

Whereas the inner circular layer of the *muscularis externa* is unremarkable, the fibers of the external longitudinal layer from the *cecum* to the *rectum* (but not in the appendix) are gathered into three bundles called the *taenia coli*. These bundles are significantly shorter than the intestinal tube in this region, which results in a gathering of the wall into the series of sacculations called *haustra*. Most of the large intestine is surrounded by a serosa.

At the level of the *rectum*, the *muscular externa* spreads out to form a coat which is a little thicker on the anterior and posterior aspects than on the sides, and, because the fibers are again somewhat shorter than the tube, causes the underlying rectal wall to bulge inward to help support the faeces and lighten the load on the anal sphincter. The inner circumferential layer of smooth muscle fibers in the *muscular externa* becomes thickened in the anal canal to form the *internal anal sphincter*. Skeletal muscle from the pelvic floor surrounds the anal canal forming the *external anal sphincter*, which is under voluntary control (Figure 6B).

At the level of the *recto-anal junction*, the crypts of Lieberkuhn end and there is a rather abrupt transition of the epithelium to a *non-keratinizing stratified squamous* variety which lines the anal canal over a distance of about 2 cm and becomes continuous with the *epidermis* (keratinized stratified squamous epithelium). Branched, tubular apocrine sweat glands are

located near the recto-anal junction. While active in some lower mammals these glands are probably vestigial in humans. The mucosa of the recto-anal canal is thrown into a series of longitudinal folds or rectal columns, which, at the distal end, are connected by horizontal folds to form anal valves (Figure 6B). In the recto-anal region the blood vasculature is characterized by many convoluted veins which, when dilated with blood, cause the mucosa to bulge into the lumen--a condition known as internal or external hemorrhoids, depending on whether the veins encroach on the canal or the anus proper.
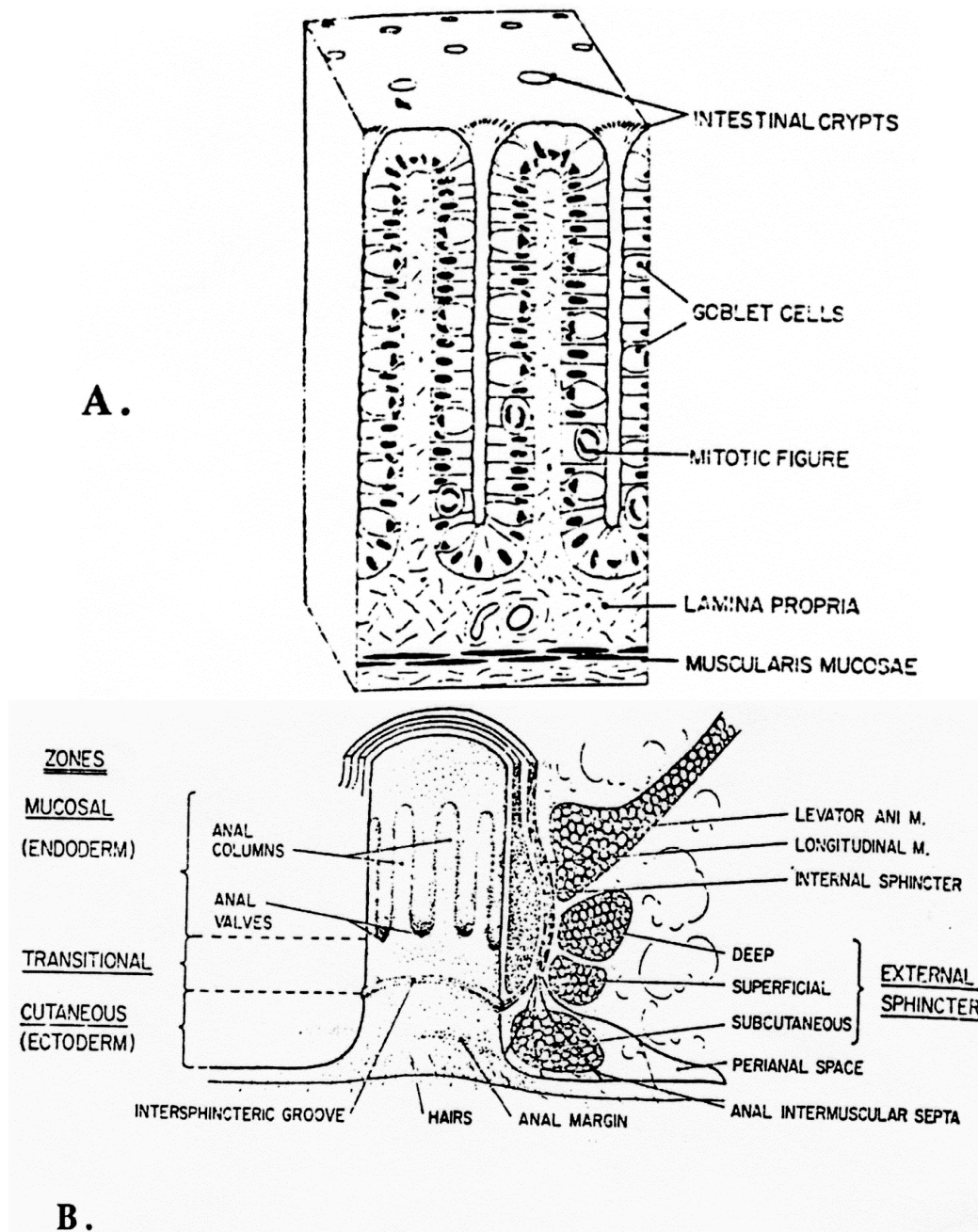

Figure 6. The large intestine: **(A)** organization of the mucosa of the colon, **(B)** the anal canal.

Tips for Webslide study

1.   Identify the four layers characteristic of the GI tract: <u>mucosa</u>, <u>submucosa</u>, <u>muscularis externa</u>, and <u>adventitia/serosa</u>. If these 4 layers are present you <u>must</u> be viewing part of the alimentary tube. (If this specific layering is not present, you are <u>not</u> examining the GI tract.)

2.   Always scan each section at <u>low power</u>. Look for obvious junctions, for example between the esophagus and stomach.

3.   Once you have identified the 4 layers of the GI tract, look for the key structural features of the specific region of the tract. For example, <u>stratified squamous epithelium</u> lines the <u>esophagus</u> and <u>anal canal</u>, whereas <u>simple columnar epithelium</u> lines the <u>stomach</u>, <u>small intestine</u>, and <u>large intestine</u>. However, these GI organs with simple columnar epithelium can be distinguished by several criteria, most importantly by differences in <u>mucosal folding</u>. There are <u>pits</u> leading into <u>coiled glands</u> in the stomach, <u>villi</u> and <u>straight glands</u> (crypts) in the small intestine, and <u>straight glands</u> (crypts) in the large intestine. Thus villi are unique to the small intestine.

4.   Cross-sectioned villi and glands will both appear as circular structures. However, in villi the surface epithelium will be seen enclosing cellular connective tissue (<u>lamina propria)</u>, whereas in glands the epithelium will ring open spaces--the lumens of the glands.

5.   If you realize by these criteria that you are examining the stomach, determine the specific region by identifying the cell types present in the glands.

6.   If you realize by these criteria that you are examining the small intestine, determine the specific region by looking for Brunner's glands (duodenum) or Peyer's Patches (ileum).

7.   Use the GI Tract Exercises in the Lab Manual to remind you of the key features of each region.

8.   As a study aid, relate structure with function. For example, absorptive cells with <u>microvillus brush borders</u> are found in the small and large intestine, where most absorption takes place, but not in the stomach.

9.   Use the orientation of the muscle layers of the <u>muscularis externa</u> to determine the plane of section for each slide. A cross-section of the tube will show longitudinally-sectioned muscle in the inner layer and cross-sectioned muscle fibers in the outer layer, whereas these relationships are reversed in a longitudinal section. (An oblique section of the tube cuts both muscle layers obliquely)