Chapter 4

GI Physiology Secretions

The sense of taste affords an animal the ability to evaluate what it eats and drinks. At the most basic level, this evaluation is to promote ingestion of nutritious substances and prevent consumption of potential poisons or toxins. There is no doubt that animals, including humans, develop taste preferences. That is, they will choose certain types of food in preference to others. Interestingly, taste preference often changes in conjunction with body needs. Similarly, animals often develop food aversions, particularly if they become ill soon after eating a certain food, even though that food was not the cause of the illness - surely you have experienced this yourself. Food preferences and aversions involve the sense of taste, but these phenomena are almost certainly mediated through the central nervous system.

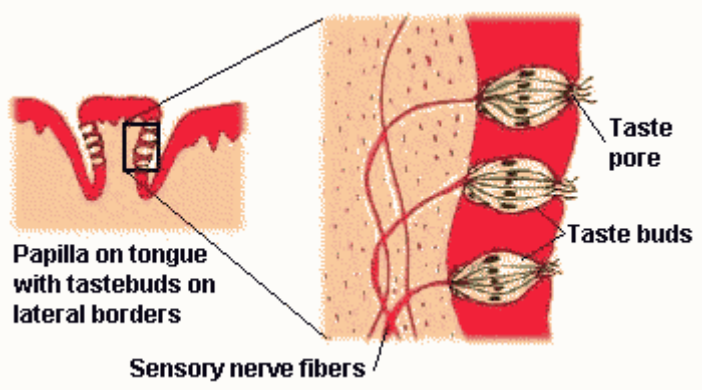
Taste Receptor Cells, Taste Buds and Taste Nerves

The sense of taste is mediated by **taste receptor cells** which are bundled in clusters called **taste buds**. Taste receptor cells sample oral concentrations of a large number of small molecules and report a sensation of taste to centers in the brainstem.

In most animals, including humans, taste buds are most prevalent on small pegs of epithelium on the tongue called papillae. The taste buds themselves are too small to see without a microscope, but papillae are readily observed by close inspection of the tongue's surface. To make them even easier to see, put a couple of drops of blue food coloring on the tongue of a loved one, and you'll see a bunch of little pale bumps - mostly fungiform papillae - stand out on a blue background.

Taste buds are composed of groups of between 50 and 150 columnar taste receptor cells bundled together like a cluster of bananas. The taste receptor cells within a bud are arranged such that their tips form a small taste pore, and through this pore extend microvilli from the taste cells. The microvilli of the taste cells bear taste receptors.

Interwoven among the taste cells in a taste bud is a network of dendrites of sensory nerves called "*taste nerves*". When taste cells are stimulated by binding of chemicals to their receptors, they depolarize and this depolarization is transmitted to the taste nerve fibers resulting in an action potential that is ultimately transmitted to the brain. One interesting aspect of this nerve transmission is that it rapidly adapts - after the initial stimulus, a strong discharge is seen in the taste nerve fibers but within a few seconds, that response diminishes to a steady-state level of much lower amplitude.



Once taste signals are transmitted to the brain, several efferent neural pathways are activated that are important to digestive function. For example, tasting food is followed rapidly by increased salivation and by low level secretory activity in the stomach.

Among humans, there is substantial difference in taste sensitivity. Roughly one in four people is a "supertaster" that is several times more sensitive to bitter and other tastes than those that taste poorly. Such differences are heritable and reflect differences in the number of fungiform papillae and hence taste buds on the tongue.

In addition to signal transduction by taste receptor cells, it is also clear that the sense of smell profoundly affects the sensation of taste. Think about how tastes are blunted and sometimes different when your sense of smell is disrupted due to a cold.

Taste Sensations

The sense of taste is equivalent to excitation of taste receptors, and receptors for a large number of specific chemicals have been identified that contribute to the reception of taste. Despite this complexity, five types of tastes are commonly recognized by humans:

- Sweet - usually indicates energy rich nutrients
- Umami - the taste of amino acids (e.g. meat broth or aged cheese)
- Salty - allows modulating diet for electrolyte balance
- Sour - typically the taste of acids
- Bitter - allows sensing of diverse natural toxins

None of these tastes are elicited by a single chemical. Also, there are thresholds for detection of taste that differ among chemicals that taste the same. For example, sucrose, 1-propyl-2 amino-4-nitrobenzene and lactose all taste sweet to humans, but the sweet taste is elicited by these chemicals at concentrations of roughly 10 mM, 2 uM and 30 mM respectively - a range of potency of roughly 15,000-fold. Substances sensed as bitter typically have very low thresholds.

Examples of some human thresholds

Taste	Substance	Threshold for tasting
Salty	NaCl	0.01 M

Sour	HCl	0.0009 M
Sweet	Sucrose	0.01 M
Bitter	Quinine	0.000008 M
Umami	Glutamate	0.0007 M

It should be noted that these tastes are based on human sensations and some comparative physiologists caution that each animal probably lives in its own "taste world". For animals, it may be more appropriate to discuss tastes as being pleasant, unpleasant or indifferent. Additionally, there are some clear differences among animals in what they can taste. Cats, for example, do not respond to sweets due to a deletion in the gene that encodes one of the sweet receptors.

Perception of taste also appears to be influenced by thermal stimulation of the tongue. In some people, warming the front of the tongue produces a clear sweet sensation, whilecooling leads to a salty or sour sensation.

Taste Receptors

A very large number of molecules elicit taste sensations through a rather small number of taste receptors. Furthermore, it appears that individual taste receptor cells bear receptors for one type of taste. In other words, within a taste bud, some taste receptor cells sense sweet, while others have receptors for bitter, sour, salty and umami tastes. Much of this understanding of taste receptors has derived from behavioral studies with mice engineered to lack one or more taste receptors.

The pleasant tastes (sweet and umami) are mediated by a family of three T1R receptors that assemble in pairs. Diverse molecules that lead to a sensation of sweet bind to a receptor formed from T1R2 and T1R3 subunits. Cats have a deletion in the gene for T1R2, explaining their non-responsiveness to sweet tastes. Also, mice engineered to express the human T1R2 protein have a human-like response to different sweet tastes. The receptor formed as a complex of T1R1 and T1R3 binds L-glutamate and L-amino acids, resulting the umami taste.

The bitter taste results from binding of diverse molecules to a family of about 30 T2R receptors. Sour tasting itself involves activation of a type of TRP (transient receptor potential) channel. Surprisingly, the molecular mechanisms of salt taste reception are poorly characterized relative to the other tastes.

Salivary Glands and Saliva

Saliva is produced in and secreted from salivary glands. The basic secretory units of salivary glands are clusters of cells called an acini. These cells secrete a fluid that contains water, electrolytes, mucus and enzymes, all of which flow out of the acinus into collecting ducts.

Within the ducts, the composition of the secretion is altered. Much of the sodium is actively reabsorbed, potassium is secreted, and large quantities of bicarbonate ion are secreted. Bicarbonate secretion is of tremendous importance to ruminants because it, along with

phosphate, provides a critical buffer that neutralizes the massive quantities of acid produced in the forestomachs. Small collecting ducts within salivary glands lead into larger ducts, eventually forming a single large duct that empties into the oral cavity.

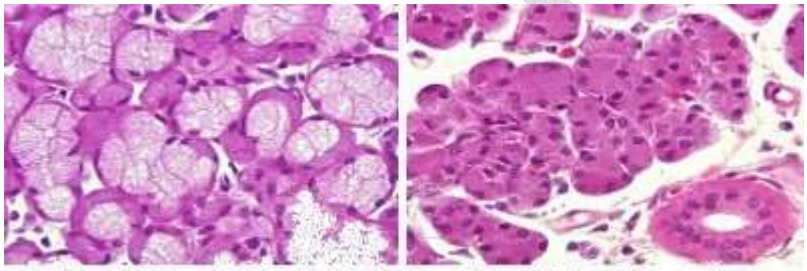
Most animals have three major pairs of salivary glands that differ in the type of secretion they produce:

- *parotid glands* produce a serous, watery secretion
- *submaxillary (mandibular) glands* produce a mixed serous and mucous secretion
- *sublingual glands* secrete a saliva that is predominantly mucous in character

The basis for different glands secreting saliva of differing composition can be seen by examining salivary glands histologically. Two basic types of acinar epithelial cells exist:

- *serous cells*, which secrete a watery fluid, essentially devoid of mucus
- *mucous cells*, which produce a very mucus-rich secretion

Acini in the parotid glands are almost exclusively of the serous type, while those in the sublingual glands are predominantly mucus cells. In the submaxillary glands, it is common to observe acini composed of both serous and mucus epithelial cells.



In the histologic sections of canine salivary gland shown above, the cells stained pink are serous cells, while the white, foamy cells are mucus-secreting cells.

Secretion of saliva is under control of the autonomic nervous system, which controls both the volume and type of saliva secreted. This is actually fairly interesting: a dog fed dry dog food produces saliva that is predominantly serous, while dogs on a meat diet secrete saliva with much more mucus. Parasympathetic stimulation from the brain, as was well demonstated by Ivan Pavlov, results in greatly enhanced secretion, as well as increased blood flow to the salivary glands.

Potent stimuli for increased salivation include the presence of food or irritating substances in the mouth, and thoughts of or the smell of food. Knowing that salivation is controlled by the brain will also help explain why many psychic stimuli also induce excessive salivation - for example, why some dogs salivate all over the house when it's thundering

What then are the important functions of saliva? Saliva serves many roles, some of which are important to all species, and others to only a few:

- *Lubrication and binding:* the mucus in saliva is extremely effective in binding masticated food into a slippery bolus that (usually) slides easily through the

esophagus without inflicting damage to the mucosa. Saliva also coats the oral cavity and esophagus, and food basically never directly touches the epithelial cells of those tissues.

- *Solubilizes dry food:* in order to be tasted, the molecules in food must be solubilized.
- *Oral hygiene:* The oral cavity is almost constantly flushed with saliva, which floats away food debris and keeps the mouth relatively clean. Flow of saliva diminishes considerably during sleep, allow populations of bacteria to build up in the mouth -- the result is *dragon breath* in the morning. Saliva also contains lysozyme, an enzyme that lyses many bacteria and prevents overgrowth of oral microbial populations.
- *Initiates starch digestion:* in most species, the serous acinar cells secrete an alpha-amylase which can begin to digest dietary starch into maltose. Amylase is not present, or present only in very small quantities, in the saliva of carnivores or cattle.
- *Provides alkaline buffering and fluid:* this is of great importance in ruminants, which have non-secretory forestomachs.
- *Evaporative cooling:* clearly of importance in dogs, which have very poorly developed sweat glands - look at a dog panting after a long run and this function will be clear.

Diseases of the salivary glands and ducts are not uncommon in animals and man, and excessive salivation is a symptom of almost any lesion in the oral cavity. The dripping of saliva seen in rabid animals is not actually a result of excessive salivation, but due to pharyngeal paralysis, which prevents saliva from being swallowed.

Prehension, Mastication, Swallowing

Prehension is the process of siezing or grasping or otherwise getting food into the mouth. Different species use different techniques to prehend food - for example, horses and goats rely considerably on their lips, whereas cattle, dogs and cats don't use their lips to any extent, but rather, gather many foods with their tongues. Studying comparative prehension can be entertaining, but is of minimal value for understanding digestion.

As with prehension, there are considerable differences among species in techniques used for drinking, that basically boil down to being either a "sucker" or a "lapper". Drinking is usually an efficient process, although beards and moustaches can sometimes interfere.

Mastication, or chewing, is the first step in the breakdown of complex foodstuffs and serves several functions, including:

- breaking large pieces into small pieces, resulting in a massive increase in surface area, which is where digestive enzymes work
- softening of food and transformation into a size conducive to swallowing
- lubrication of food by impregnating it with saliva

Chewing is, to a large extent, a reflex, although you can voluntarily masticate as well. To study this phenomenon, watch a cow ruminating or look around and watch someone chewing gum. The presence of food (or gum) in the mouth causes a reflex inhibition of the muscles of the lower jaw. Those muscles relax and the lower jaw drops, causing a stretch reflex which causes muscle contraction and closure of the mouth. During mastication, the tongue and, to a lesser extent, the lips and cheeks acts to keep food between the grinding surfaces of the teeth. This can be demonstrated by trying to chew your next meal while

holding your tongue still. Incidentally, chewing is hard work and expends a lot of energy.

Deficits in the ability to effectively masticate are a very common cause of digestive disease in animals. Many of these problems are associated with poor teeth, and most are easily diagnosed by simple inspection. A particularly common problem in horses is the occurence of "points" on the molar teeth.

The final step in pregastric digestion is swallowing, also known as deglutition. This is really a very complex process that can be thought of as occurring in three steps:

- First, a bolus of food is pressed backward into the pharynx by the tongue. This is the only step that is voluntary - the remaining steps occur by reflex.
- Once the bolus reaches the pharynx several actions are initiated, which basically involve shunting the bolus into the esophagus while at the same time closing alternative routes of escape. The lumen of the larynx is squeezed shut and the epiglottis swings backward to cover the larynx. The larynx is also pulled forward and down making the opening to the esophagus larger.
- Finally, the tongue presses backward and a peristaltic contraction in the pharynx propels the bolus into the esophagus, where the actual act of swallowing takes place.

During swallowing, boluses of food are propelled through the esophagus by strong peristaltic contractions. In dogs and humans, it takes 4-5 seconds for the bolus to traverse the esophagus. If the bolus is not delivered in "one pass", secondary waves of peristalsis are initiated at the point of distention, which almost always result in delivery of the bolus to the stomach. Congenital and acquired disorders in esophageal motility that interfere with this usually reliable delivery of food are rather common in both animals and man.

The Esophagus

Anatomically and functionally, the esophagus is the least complex section of the digestive tube. Its role in digestion is simple: to convey boluses of food from the pharynx to the stomach. The esophagus begins as an extension of the pharynx in the back of the oral cavity. It then courses down the neck next to the trachea, through the thoracic cavity, and penetrates the diaphragm to connect with the stomach in the abdominal cavity.

Like other parts of the digestive tube, the esophagus has four tunics, but important differences exist in the composition of these tunics in comparison to more distal sections of the tube. First, instead of the muscular tunic being entirely smooth muscle, as it is in the stomach and intestines, the wall of the esophagus contains a variable amount of striated muscle. In dogs, cattle and sheep, its entire length is striated muscle, whereas in cats, horses and humans, the proximal esophagus has striated muscle and the distal esophagus smooth muscle. Second, instead of the esophagus being free as it courses through the thoracic cavity, it is embedded in the connective tissue; thus, its outer tunic is referred to as adventitia instead of serosa.

In its role as the first conduit in the digestive tube, the esophagus is routinely exposed to rough and abrasive foodstuffs, like fragments of bone, fibrous plant leaves and Doritos. Its

surface should therefore be resistant to trauma, and indeed, the esophagus is lined with *stratified squamous epithelium*, as seen below in an image from a cat's esophagus:

Absorption in the esophagus is virtually nil. The mucosa does contain mucous glands that are expressed as foodstuffs distend the esophagus, allowing mucus to be secreted and aid in lubrication.

The body of the esophagus is bounded by physiologic sphincters known as the upper and lower esophageal sphincters. The upper sphincter is composed largely of a muscle that is closely associated with the larynx. When relaxed, as it is during swallowing, this muscle pulls the larynx forward and aids in routing food into the esophagus instead of the larynx. The lower esophageal sphincter is the muscle that surrounds the esophagus just as it enters the stomach.

Normally, the upper and lower sphincters are closed except during swallowing, which prevents constant entry of air from the oral cavity or reflux of stomach contents. In humans, common disorders involving the esophagus include heartburn and gastroesophageal reflux disease (GERD). In both cases, the lower sphincter does not close properly, allowing acid from the stomach to reflux back into the esophagus, causes a burning sensation in the chest or throat (heartburn) or additional signs such as coughing, coughing or a sensation of choking.

An associated problem is *acid indigestion*, which occurs when refluxed stomach acid is tasted. Occasional heartburn is very common, but if it occurs more than a time or two each week, it could signify a more serious problem that requires treatment, usually with dietary managment and drugs that suppress secretion of gastric acid.

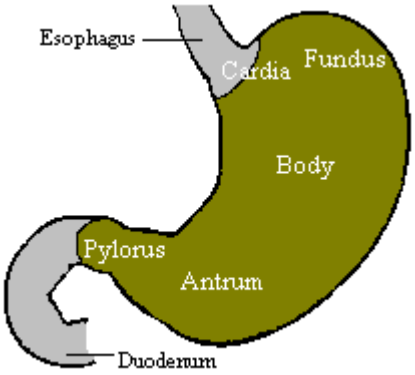
The Stomach: Introduction and Index

Foodstuffs entering the stomach have been, to at least some extent, crushed and reduced in size by mastication, and impregnanted with saliva. The stomach provides four basic functions that assist in the early stages of digestion and prepare the ingesta for further processing in the small intestine:

1. It serves as a **short-term storage reservoir**, allowing a rather large meal to be consumed quickly and dealt with over an extended period of time.
2. It is in the stomach that **substantial enzymatic digestion** is initiated, particularly of proteins.
3. Vigorous contractions of gastric smooth muscle mix and grind foodstuffs with gastric secretions, resulting in **liquefaction of food**, a prerequisite for delivery of the ingesta to the small intestine.
4. As food is liquefied in the stomach, it is **slowly released into the small intestine**for further processing.

Gross and Microscopic Anatomy of the Stomach

The stomach is an expanded section of the digestive tube between the esophagus and small intestine. It's characteristic shape is shown, along with terms used to describe the major regions of the stomach. The right side of the stomach shown above is called the greater curvature and that on the left the lesser curvature. The most distal and narrow section of the stomach is termed the*pylorus* - as food is liquefied in the stomach it passes through the pyloric canal into the small intestine.



The wall of the stomach is structurally similar to other parts of the digestive tube, with the exception that the stomach has an extra, oblique layer of smooth muscle inside the circular layer, which aids in performance of complex grinding motions.

In the empty state, the stomach is contracted and its mucosa and submucosa are thrown up into distinct folds called **rugae**; when distended with food, the rugae are "ironed out" and flat. The image to the right shows rugae on the surface of a dog's stomach.

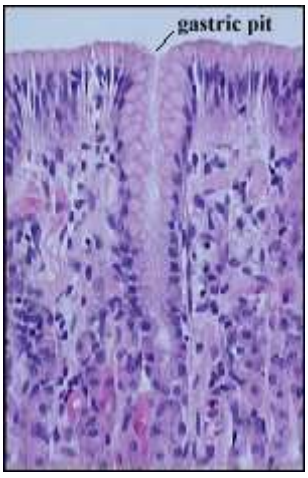
Within the stomach there is an abrupt transition from stratified squamous epithelium extending from the esophagus to a columnar epithelium dedicated to secretion. In most species, this transition is very close to the esophageal orifice, but in some, particular horses and rodents, stratified squamous cells line much of the fundus and part of the body.

The image to the right is of the mucosal surface of an equine stomach showing esophageal epithelium (top) and glandular epithelium (bottom). The creatures attached to the surface are bots, larval forms of *Gasterophilus*.

If the lining of the stomach is examined with a hand lens, one can see that it is covered with numerous small holes. These are the openings of *gastric pits* which extend into the mucosa as straight and branched tubules, forming gastric glands.

Four major types of secretory epithelial cells cover the surface of the stomach and extend down into gastric pits and glands:

- **Mucous cells**: secrete an *alkaline mucus* that protects the epithelium against shear stress and acid
- **Parietal cells**: secrete *hydrochloric acid*
- **Chief cells**: secrete *pepsin*, a proteolytic enzyme
- **G cells**: secrete the hormone *gastrin*



There are differences in the distribution of these cell types among regions of the stomach - for example, parietal cells are abundant in the glands of the body, but virtually absent in pyloric glands. The micrograph to the right shows a gastric pit invaginating into the mucosa (fundic region of a raccoon stomach). Notice that all the surface cells and the cells in the

neck of the pit are foamy in appearance - these are the mucous cells. The other cell types are farther down in the pit and, in this image, difficult to distinguish.

Here's an interesting piece of trivia about the stomach: the platypus does not have one. In this strange mammal, the distal esophagus is dilated, but the platypus does not have a glandular stomach. Moreover, its genome has deletions of some of the key genes involved in gastric sections, including those for pepsinogens, the gastric H+/K+ ATPase(proton pump) and the hormone gastrin.

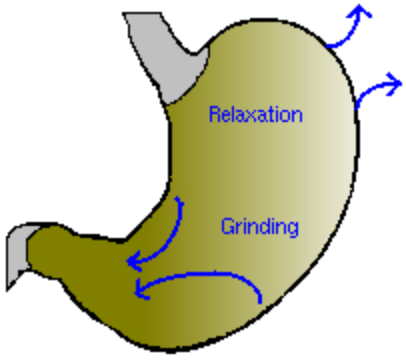
Gastric Motility: Filling and Emptying

Contractions of gastric smooth muscle serves two basic functions:

- ingested food is crushed, ground and mixed, liquefying it to form what is called*chyme*.
- chyme is forced through the pyloric canal into the small intestine, a process called gastric emptying.

The stomach can be divided into two regions on the basis of motility pattern: an accordian-like reservoir that applies constant pressure on the lumen and a highly contractile grinder.

The upper stomach, composed of the fundus and upper body, shows low frequency, sustained contractions that are responsible for generating a basal pressure within the stomach. Importantly, these tonic contractions also generate a pressure gradient from the stomach to small intestine and are thus responsible for gastric emptrying. Interestingly, swallowing of food and consequent gastric distention inhibits contraction of this region of the stomach, allowing it to balloon out and form a large reservoir without a significant increase in pressure.



The lower stomach, composed of the lower body and antrum, develops strong peristaltic waves of contraction that increase in amplitude as they propagate toward the pylorus. These powerful contractions constitute a very effective gastric grinder; they occur about 3 times per minute in people and 5 to 6 times per minute in dogs. Gastric distention strongly stimulates this type of contraction, accelerating liquefaction and hence, gastric emptying. The pylorus is functionally part of this region of the stomach - when the peristaltic contraction reaches the pylorus, its lumen is effectively obliterated - chyme is thus delivered to the small intestine in spurts.

Gastric motility is controlled by a very complex set of neural and hormonal signals. Nervous

control originates from the enteric nervous system as well as parasympathetic (predominantly vagus nerve) and sympathetic systems. A large battery of hormones have been shown to influence gastric motility - for example, both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach. The bottom line is that the patterns of gastric motility likely are a result from smooth muscle cells integrating a large number of inhibitory and stimulatory signals.

Liquids readily pass through the pylorus in spurts, but solids must be reduced to a diameter of less than 1-2 mm before passing the pyloric gatekeeper. Larger solids are propelled by peristalsis toward the pylorus, but then refluxed backwards when they fail to pass through the pylorus - this continues until they are reduced in size sufficiently to flow through the pylorus.

At this point, you may be asking *"What happens to solids that are indigestible - for example, a rock or a penny? Will it remain forever in the stomach?"* If the indigestible solids are large enough, they indeed cannot pass into the small intestine, and will either remain in the stomach for long periods, induce a gastric obstruction or, as every cat owner knows, be evacuated by vomition. However, many of the indigestible solids that fail to pass through the pylorus shortly after a meal do pass into the small intestine during periods between meals. This is due to a different pattern of motor activity called themigrating motor complex, a pattern of smooth muscle contractions that originates in the stomach, propagates through the intestines and serves a housekeeping function to periodically sweep out the gastrointestinal tract.

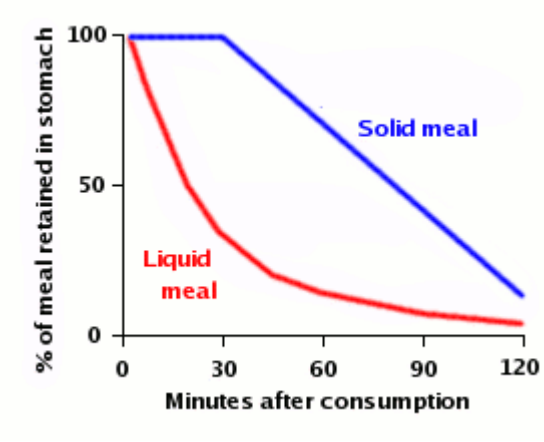
Control of Gastric Emptying

The rate of gastric emptying is strongly influenced by both volume and composition of gastric contents, which makes considerable sense. Consider three examples of something you might ingest and try to anticipate which rate of gastric emptying would be most appropriate:

A large glass of water: The stomach becomes distended, but there are no solids to grind and liquefy, and after the water reaches the small intestine, no further processing is required before absorption - the rate of gastric emptying should be very fast.

A double cheeseburger with fries (or a mouse if you're a cat): The stomach is distended and its contents must be liquefied; you would also want the meal to be retained in the stomach long enough for pepsin and acid to get a good shot at digesting the protein. Additionally, the resulting chyme should be allowed to empty in the small intestine slowly so as to not overload that organ, particularly with regard to digestion of fat - the rate of gastric emptying should be slow.

A single chicken nugget (or a grasshopper if you're a cat): The stomach will not be distended after this kind of a "meal" and in the absense of distension, there is relatively little stimulus for gastric motility - the rate of gastric emptying should be slow.



After consuming a typical solid meal, there is a lag time of 20 to 30 minutes in which there is minimal gastric emptying. This is followed by a phase in which the rate of emptying is roughly linear. In contrast, liquids are generally transported out of the stomach at an exponential rate.

For liquids, the principal determinant of rate of gastric emptying is volume and, secondarily, composition. If the liquid is low in nutrients (e.g. water), there is an exponential relationship between volume and rate of emptying - large volumes empty at an exponentially faster rate than small volumes.

However, if the fluid is hypertonic or acidic or rich in nutrients such as fat or certain amino acids, the rate of gastric emptying will be considerably slower and non-exponential. Indeed, the rate of gastric emptying of any meal can be predicted rather accurately by knowing its nutrient density. Nutrient density is sensed predominantly in the small intestine by osmoreceptors and chemoreceptors, and relayed to the stomach as inhibitory neural and hormonal messages that delay emptying by altering the patterns of gastric motility. The presence of fat in the small intestine is the most potent inhibitor of gastric emptying, resulting in relaxation of the proximal stomach and diminished contractions of the distal, "gastric grinder" - when the fat has been absorbed, the inhibitory stimulus is removed and productive gastric motility resumes.

Understanding the basic principles of gastric emptying facilitates management of gastric motility disorders, which are relatively common in both man and animals.

Gastrointestinal Transit: How Long Does It Take?

How long does food stay in my stomach? How long is it before a meal reaches the large intestine? *The answer to such commonly-asked questions is not necessarily simple.*

First, there is considerable normal variability among healthy people and animals in transit times through different sections of the gatrointestinal tract. Second, the time required for material to move through the digestive tube is significantly affected by the composition of the meal. Finally, transit time is influenced by such factors as psychological stress and even gender and reproductive status.

Several techniques have been used to measure transit times in humans and animals. Not surprisingly, differing estimates have been reported depending on the technique used and the population of subjects being evaluated. Some of the techniques used include:

- *Radiography following a barium-labelled meal.* Sequential radiographs can be used to determine when the front of the barium label reaches different regions of the digestive tube. Such meals are not very physiologic and the technique exposes the patient to repeated exposure to radiation.

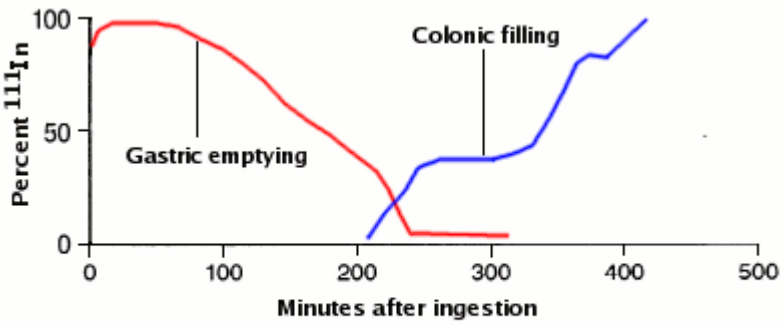
- *Breath hydrogen analysis.* A number of carbohydrates are very poorly digested or absorbed in the small intestine, but readily fermented by bacteria when they reach the large intestine. Fermentation liberates hydrogen gas, which diffuses into blood and is exhaled in breath, where it can be readily measured. Thus, after consumption of a meal containing a non-absorbable carbohydrate (lactulose or, more commonly, baked beans), there is a large increase in exhaled hydrogen when the carbohydrate reaches the large intestine. This provides an estimate of pre-colonic (stomach plus small intestine) transit time.
- *Scintigraphic analyses.* Meals containing pellets or colloids labelled with a small amount of radionuclide (^{99m}Technetium, ^{113m}Indium, etc.) are consumed, and the position of the radioactive label is sequentially monitored using a gamma camera.

Studies of gastrointestinal transit have clearly demonstrated two related phenomena important to understanding this process:

1. Substances do not move uniformly through the digestive system.
2. Materials do not leave segments of the digestive tube in the same order as they arrive.

In other words, a meal is typically a mixture of chemically and physically diverse materials, and some substances in this mixture show accelerated transit while others are retarded in their flow downstream.

An example of how ingested substances spread out in the digestive tube rather than travel synchronously is shown in the figure below. These data were obtained from a human volunteer that ingested a meal containing ^{111}Indium-labeled pellets, then measuring the location of the radioactive signal over time by scintigraphy. It is clear that parts of the meal are entering the colon at the same time that other parts are still in the stomach.



(Adapted from Camilleri, et al. Am J Physiol Gastrointest Liver Physiol 257:284, 1989.)

The discussion above should help to explain why it is difficult to state with any precision how long ingesta remains in the stomach, small intestine and large intestine. Nonetheless, there have been many studies on GI transit, and the table below presents rough estimates for transit times in healthy humans following ingestion of a standard meal (i.e. solid, mixed foods).

50% of stomach contents emptied	2.5 to 3 hours
Total emptying of the stomach	4 to 5 hours
50% emptying of the small intestine	2.5 to 3 hours
Transit through the colon	30 to 40 hours

Remember that these are estimtes of average transit times, and there is a great deal of variability among individuals and in the small person at different times and after different meals.

The Migrating Motor Complex

The migrating motor complex is a distinct pattern of electromechanical activity observed in gastrointestinal smooth muscle during the periods between meals. It is thought to serve a "housekeeping" role and sweep residual undigested material through the digestive tube. As studied in dogs and man, the cycle recurs every 1.5 to 2 hours and consists of 4 phases:

1. A period of smooth muscle quiescence lasting 45 to 60 minutes, during which there are only rare action potentials and contractions.
2. A period of roughly 30 minutes in which peristaltic contractions occur and progressively increase in frequency. Peristalsis originates in the stomach and propagates through the small intestine.
3. The phase lasting 5 to 15 minutes in which rapid, evenly spaced peristaltic contractions occur. In contrast to the digestive period, the pylorus remains open during these peristaltic contractions, allowing many indigestible materials to pass into the small intestine.
4. A short period of transition between the barrage of contractions in phase 3 and the inactivity of phase 1.

An increase in gastric, biliary and pancreatic secretion is also seen in conjunction with the motor activity. These secretions probably aid in the cleansing activity of the migrating motor complex and assist in preventing a buildup of bacterial populations in the proximal segments of the digestive tube.

The periodic nature of the migrating motor complex is thought to be controlled from the central nervous system and may be implemented in part by the enteric hormone motilin. Like real housekeeping, the migrating motor complex is readily overridden by "more important" processes - for example, ingestion of food will abolish a migrating motor complex and restore a digestive pattern of motility.

Aside from its apparent importance in maintaining patency of the gastrointestinal lumen, the migrating motor complex has potentially important theraputic and social implications:

- Blood levels of drugs that are differentially absorbed in the stomach and small intestine may vary unpredictably depending on whether they are taken during digestive or interdigestive phases, when mechanisms of gastric emptying are different - this is reflected in the recommendation accompanying many drugs to ingest before or with meals.

- Migrating motor complexes can be noisy and are the cause of "*growling*." Fortunately, you can usually squelch a migrating motor complex by ingesting some food, allowing transition into a quiet, digestive pattern of motility. If food is not available (let's say you're undergoing a job interview or waiting in line with your date at a concert), you can at least explain the phenomenon and gain points for intellect.

Physiology of Vomiting

Vomiting is the forceful expulsion of contents of the stomach and often, the proximal small intestine. It is a manifestation of a large number of conditions, many of which are not primary disorders of the gastrointestinal tract. Regardless of cause, vomiting can have serious consequences, including acid-base derangments, volume and electrolyte depletion, malnutrition and aspiration pneumonia.

The Act of Vomiting

Vomiting is usually experienced as the finale in a series of three events, which everyone reading this has experienced:

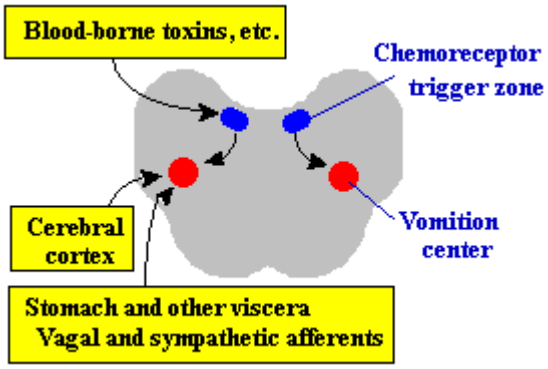
- **Nausea** is an unpleasant and difficult to describe psychic experience in humans and probably animals. Physiologically, nausea is typically associated with decreased gastric motility and increased tone in the small intestine. Additionally, there is often reverse peristalsis in the proximal small intestine.
- **Retching** ("dry heaves") refers to spasmodic respiratory movements conducted with a closed glottis. While this is occurring, the antrum of the stomach contracts and the fundus and cardia relax. Studies with cats have shown that during retching there is repeated herniation of the abdominal esophagus and cardia into the thoracic cavity due to the negative pressure engendered by inspiratory efforts with a closed glottis.
- **Emesis or vomition** is when gastric and often small intestinal contents are propelled up to and out of the mouth. It results from a highly coordinated series of events that could be described as the following series of steps (don't practice these in public):
    - A deep breath is taken, the glottis is closed and the larynx is raised to open the upper esophageal sphincter. Also, the soft palate is elevated to close off the posterior nares.
    - The diaphragm is contracted sharply downward to create negative pressure in the thorax, which facilitates opening of the esophagus and distal esophageal sphincter.
    - Simultaneously with downward movement of the diaphragm, the muscles of the abdominal walls are vigorously contracted, squeezing the stomach and thus elevating intragastric pressure. With the pylorus closed and the esophagus relatively open, the route of exit is clear.

The series of events described seems to be typical for humans and many animals, but is not inevitable. Vomition occasionally occurs abruptly and in the absense of premonitory signs - this situation is often referred to as *projectile vomiting*. A common cause of projectile vomiting is gastric outlet obstruction, often a result of the ingestion of foreign bodies.

An activity related to but clearly distinct from vomiting is *regurgitation*, which is the passive expulsion of ingested material out of the mouth - this often occurs even before the ingesta has reached the stomach and is usually a result of esophageal disease. Regurgitation also is a normal component of digestion in ruminants.

There is also considerable variability among species in the propensity for vomition. Rats reportedly do not vomit. Cattle and horses vomit rarely - this is usually an ominous sign and most frequently a result of acute gastric distension. Carnivores such as dogs and cats vomit frequently, often in response to such trivial stimuli as finding themselves on a clean carpet. Humans fall between these extremes, and interestingly, rare individuals have been identified that seem to be incapable of vomiting due to congenital abnormalities in the vomition centers of the brainstem.

Control of Vomition



The complex, almost sterotypical set of activities that culminate in vomiting suggest that control is central, which indeed has been shown to be true. Within the brainstem are two anatomically and functionally distinct units that control vomiting:

Bilateral vomition centers in the reticular formation of the medulla integrate signals from a large number of outlying sources and their excitement is ultimately what triggers vomition. Electric stimulation of these centers induces vomiting, while destruction of the vomition centers renders animals very resistant to emetic drugs. The vomition centers receive afferent signals from at least four major sources:

- **The chemoreceptor trigger zone** (see below)
- **Visceral afferents from the gastrointestinal tract** (vagus or sympathetic nerves) - these signals inform the brain of such conditions as gastrointestinal distention (a very potent stimulus for vomition) and mucosal irritation.
- **Visceral afferents from outside the gastrointestinal tract** - this includes signals from bile ducts, peritoneum, heart and a variety of other organs. These inputs to the vomition center help explain how, for example, a stone in the common bile duct can result in vomiting.
- **Afferents from extramedullary centers in the brain** - it is clear that certain psychic stimuli (odors, fear), vestibular disturbances (motion sickness) and cerebral trauma can result in vomition.

The chemoreceptor trigger zone is a bilateral set of centers in the brainstem lying under the floor of the fourth ventricle. Electrical stimulation of these centers does not induce vomiting, but application of emetic drugs does - if and only if the vomition centers are intact. The chemoreceptor trigger zones function as emetic chemoreceptors for the vomition centers - chemical abnormalities in the body (e.g. emetic drugs, uremia, hypoxia and diabetic

ketoacidosis) are sensed by these centers, which then send excitatory signs to the vomition centers. Many of the antiemetic drugs act at the level of the chemoreceptor trigger zone.

To summarize, two basic sets of pathways - one neural and one humoral - lead to activation of centers in the brain that initiate and control vomition. Think of the vomition centers as commander in chief of vomition, who makes the ultimate decision. This decision is based on input from a battery of advisors, among whom the chemoreceptor trigger zone has considerable influence. This straighforward picture is almost certainly oversimplified and flawed in some details, but helps to explain much of the physiology and pharmacology of vomition.

Causes and Consequences of Vomiting

The myriad causes of vomiting are left as an exercise - come up with a list based on personal experience and your understanding of the control of vomition. *An important point, however, is that many cases of vomiting are due to diseases outside of the gastrointestinal tract.*

Simple vomiting rarely causes problems, but on occasion, can lead to such serious consequences as aspiration pneumonia. Additionally, severe or repetitive vomition results in disturbances in acid-base balance, dehydration and electrolyte depletion. In such cases, the goal is to rapidly establish a definitive diagnosis of the underlying disease so that specific therapy can be instituted. This is often not easy and in many cases, it is advantageous to administer antiemetic drugs in order to suppress vomition and reduce its sequelae.

Gastric Secretions

The stomach is famous for its secretion of acid, but acid is only one of four major secretory products of the gastric epithelium, all of which are important either to the digestive process or to control of gastric function:

- **Mucus:** The most abundant epithelial cells are mucous cells, which cover the entire lumenal surface and extend down into the glands as "mucous neck cells". These cells secrete a bicarbonate-rich mucus that coats and lubricates the gastric surface, and serves an important role in protecting the epithelium from acid and other chemical insults.
- **Acid:** Hydrochloric acid is secreted from parietal cells into the lumen where it establishes an extremely acidic environment. This acid is important for activation of pepsinogen and inactivation of ingested microorganisms such as bacteria.
- **Proteases:** Pepsinogen, an inactive zymogen, is secreted into gastric juice from both mucous cells and chief cells. Once secreted, pepsinogen is activated by stomach acid into the active protease pepsin, which is largely responsible for the stomach's ability to initiate digestion of proteins. In young animals, chief cells also secrete chymosin (rennin), a protease that coagulates milk protein allowing it to be retained more than briefly in the stomach.
- **Hormones:** The principal hormone secreted from the gastric epithelium is gastrin, a peptide that is important in control of acid secretion and gastric motility.

A number of other enzymes are secreted by gastric epithelial cells, including a lipase and gelatinase. One secretory product of considerable importance in man is intrinsic factor, a

glycoprotein secreted by parietal cells that is necessary for intestinal absorption of vitamin B_{12}.

The Parietal Cell: Mechanism of Acid Secretion

The best-known component of gastric juice is hydrochloric acid, the secretory product of the parietal, or oxyntic cell. It is known that the capacity of the stomach to secrete HCl is almost linearly related to parietal cell numbers.

When stimulated, parietal cells secrete HCl at a concentration of roughly 160 mM (equivalent to a pH of 0.8). The acid is secreted into large cannaliculi, deep invaginations of the plasma membrane which are continuous with the lumen of the stomach.

When acid secretion is stimulated there is a dramatic change in the morphology of the membranes of the parietal cell. Cytoplasmic tubulovesicular membranes which are abundant in the resting cell virtually disappear in concert with a large increase in the cannalicular membrane. It appears that the proton pump as well as potassium and chloride conductance channels initially reside on intracellular membranes and are transported to and fused into the cannalicular membrane just prior to acid secretion.

The epithelium of the stomach is intrinsically resistant to the damaging effects of gastric acid and other insults. Nonetheless, excessive secretion of gastric acid is a major problem in human and, to a lesser extent, animal populations, leading to gastritis, gastric ulcers and peptic acid disease. As a consequence, the parietal cell and the mechanisms it uses to secrete acid have been studied extensively, leading to development of several drugs useful for suppressing acid secretion.

Mechanism of Acid Secretion

The hydrogen ion concentration in parietal cell secretions is roughly 3 million fold higher than in blood, and chloride is secreted against both a concentration and electric gradient. Thus, the ability of the partietal cell to secrete acid is dependent on active transport.

The key player in acid secretion is a H+/K+ ATPase or "proton pump" located in the cannalicular membrane. This ATPase is magnesium-dependent, and not inhibitable by ouabain. The current model for explaining acid secretion is as follows:

- Hydrogen ions are generated within the parietal cell from dissociation of water. The hydroxyl ions formed in this process rapidly combine with carbon dioxide to form bicarbonate ion, a reaction cataylzed by carbonic anhydrase.
- Bicarbonate is transported out of the basolateral membrane in exchange for chloride. The outflow of bicarbonate into blood results in a slight elevation of blood pH known as the "alkaline tide". This process serves to maintain intracellular pH in the parietal cell.
- Chloride and potassium ions are transported into the lumen of the cannaliculus by conductance channels, and such is necessary for secretion of acid.
- Hydrogen ion is pumped out of the cell, into the lumen, in exchange for potassium through the action of the proton pump; potassium is thus effectively recycled.
- Accumulation of osmotically-active hydrogen ion in the cannaliculus generates an osmotic gradient across the membrane that results in outward diffusion of water - the resulting gastric juice is 155 mM HCl and 15 mM KCl with a small amount of NaCl.

These processes are depicted in the animation below.

Control of Acid Secretion

Parietal cells bear receptors for three stimulators of acid secretion, reflecting a triumverate of neural, paracrine and endocrine control:

- **Acetylcholine** (muscarinic type receptor)
- **Gastrin**
- **Histamine** (H2 type receptor)

Histamine from enterochromaffin-like cells may well be the primary modulator, but the magnitude of the stimulus appears to result from a complex additive or multiplicative interaction of signals of each type. For example, the low amounts of histamine released constantly from mast cells in the gastric mucosa only weakly stimulate acid secretion, and similarly for low levels of gastrin or acetylcholine. However, when low levels of each are present, acid secretion is strongly forced. Additionally, pharmacologic antagonists of each of these molecules can block acid secretion.

Histamine's effect on the parietal cell is to activate adenylate cyclase, leading to elevation of intracellular cyclic AMP concentrations and activation of protein kinase A (PKA). One effect of PKA activation is phosphorylation of cytoskeletal proteins involved in transport of the H+/K+ ATPase from cytoplasm to plasma membrane. Binding of acetylcholine and gastrin both result in elevation of intracellular calcium concentrations.

The animation below depicts acid secretion by the parietal cell. Even though many of the actors are unlabeled, you should be able to deduce the identity of all the components you see.

Several additional mediators have been shown to result in gastric acid secretion when infused into animals and people, including calcium, enkephalin and bombesin. Calcium and bombesin both simulate gastrin release, while opiate receptors have been identified on parietal cells. It is unclear whether these molecules have a significant physiologic role in parietal cell function.

A variety of substances are capable of reducing gastric acid secretion when infused intravenously, including prostaglandin E_2 and several peptides hormones, includingsecretin, gastric inhibitory peptide, glucagon and somatostatin. PGE_2, secretin and somatostatin may be physiologic regulators. Somatostatin inhibits secretion of gastrin and histamine, and appears to have a direct inhibitory effect on the parietal cell.

Drug Therapy for Suppressing Secretion of Gastric Acid

development of several drugs capable of inhibiting acid secretion. These drugs are widely used in humans for treatment of acid reflux disorders such as heartburn and gastroesophageal reflux disease. The most effective inhibitors fall into two classes.

H_2 Receptor Antagonists

Histamine is clearly one of the primary regulators of acid secretion, and the parietal cell receptor for histamine is of the H2 type. Evidence of histamine's role in acid secretion is strongly supported by finding that H2 receptor antagonists are quite effective in inhibiting acid secretion. Examples of H2 antagonists commonly used to suppress gastric acid secretion include cimetidine (Tagamet HB), ranitidine (Zantac 75), famotidine (Pepcid AC) and nizatidine (Axid AR).

These drugs, particularly cimetidine, are among the most widely prescribed drugs in man. They are also useful for management of certain gastric diseases in dogs and horses. Antihistamines that engage H1 receptors (e.g. those used to treat colds) have no effect on acid secretion.

Proton Pump Inhibitors

Acid secretion is absolutely dependent on function of the H+/K+ ATPase or proton pump located in the cannilicular membrane of the parietal cell. Several drugs have been developed that non-competively bind and inactivate the ATPase, resulting in strong inhibition of acid secretion. Omeprazole (Prilosec) is an acid-activated prodrug that binds covalently to two cysteines on the ATPase, resulting in its irreversible inactivation. Other inhibitors, including lansoprazole (Prevacid), esomeprazole (Nexium), rabeprazole (Aciphex) and pantoprazole (Protonix) have similar modes of action.

Pepsinogens and Pepsins

Pepsins are the principal proteases in gastric secretions of adult mammals. They are members of the family of aspartic proteases, and closely related to chymosin, another gastric protease expressed particularly in young animals. These enzymes are synthesized and secreted predominantly by chief cells in the gastric mucosa.

At least 8 isozymes of pepsinogen have been identified in gastric epithelial cells, and these have been categorized into two immunologically-separable types (pepsins A and C). The mature, active enzymes are roughly 325 amino acids with a mass of approximately 35 kDa.

Pepsins are synthesized as inactive pre-proenzymes, consisting of a signal peptide, activation peptide and active enzyme. The signal peptide is cleaved as the protein is inserted into endoplasmic reticulum and the resulting proenzyme - pepsinogen - is transported to the Golgi and condensed into secretory granules.

Pepsinogens are secreted in a form such that the activation peptide assumes a compact structure that occludes the active site. On exposure to an acidic (pH Structurally, the active site is located in a deep cleft within the molecule. Optimal activity of pepsins is at pH of 1.8 to 3.5, depending on the isoform. They are reversibly inactivated at about pH 5 and irreversibly inactivated at pH 7 to 8.

In general, secretion of pepsinogens is coupled to secretion of acid from the parietal cell. In vitro studies have demonstrated that secretion is effectively stimulated by agents that stimulate either of two conditions:

- Elevated intracellular levels of cyclic AMP: examples include secretin, vasoactive intestinal peptide and epinephrine.
- Elevated intracellular calcium: the principal mediators investigated include acetylcholine and peptides of the gastrin/cholecystokinin family

Receptors for many of the hormones listed above have been demonstrated on chief cells and pepsinogen secretion has been stimulated or blocked by exposure to these agents or their antagonists, respectively. At the present time it seems safe to say that the principal physiologic secretagogue(s) regulating pepsinogen secretion has not been clearly deliniated.

Chymosin (Rennin) and the Coagulation of Milk

Chymosin, known also as rennin, is a proteolytic enzyme synthesized by chief cells in the stomach. Its role in digestion is to curdle or coagulate milk in the stomach, a process of considerable importance in the very young animal. If milk were not coagulated, it would rapidly flow through the stomach and miss the opportunity for initial digestion of its proteins.

Chymosin efficiently converts liquid milk to a semisolid like cottage cheese, allowing it to be retained for longer periods in the stomach. Chymosin secretion is maximal during the first few days after birth, and declines thereafter, replaced in effect by secretion of pepsinas the major gastric protease.

Chymosin is secreted as an inactive proenzyme called prochymosin that, like pepsin, is activated on exposure to acid. Chymosin is also similar to pepsin in being most active in acidic environments, which makes sense considering its mission.

In order to understand how chymosin coagulates milk, one needs to know something about milk proteins. The majority of milk protein is casein and there are four major types of casein molecules: alpha-s1, alpha-s2, beta and kappa. The alpha and beta caseins are hydrophobic proteins that are readily precipitated by calcium - the normal calcium concentration in milk is far in excess of that required to precipitate these proteins. However, kappa casein is a distinctly different molecule - it is not calcium-precipitable. As the caseins are secreted, they self-associate into aggregates called micelles in which the alpha and beta caseins are kept from precipitating by their interactions with kappa casein. In essence, kappa casein normally keeps the majority of milk protein soluble and prevents it from spontaneously coagulating.

Enter chymosin. Chymosin proteolytically cuts and inactivates kappa casein, converting it into para-kappa-casein and a smaller protein called macropeptide. Para-kappa-casein does not have the ability to stabilize the micellar structure and the calcium-insoluble caseins precipitate, forming a curd.

Aside from its physiologic role, chymosin is also a very important industrial enzyme because it is widely used in cheesemaking. In days gone by, chymosin was extracted from dried calf stomachs for this purpose, but the cheesemaking industry has expanded beyond the supply of available calf stomachs (remember that these have to be from young calves). It turns out that many proteases are able to coagulate milk by converting casein to paracasein and alternatives to chymosin are readily available. "Rennet" is the name given to any enzymatic preparation that clots milk.

Intrinsic Factor

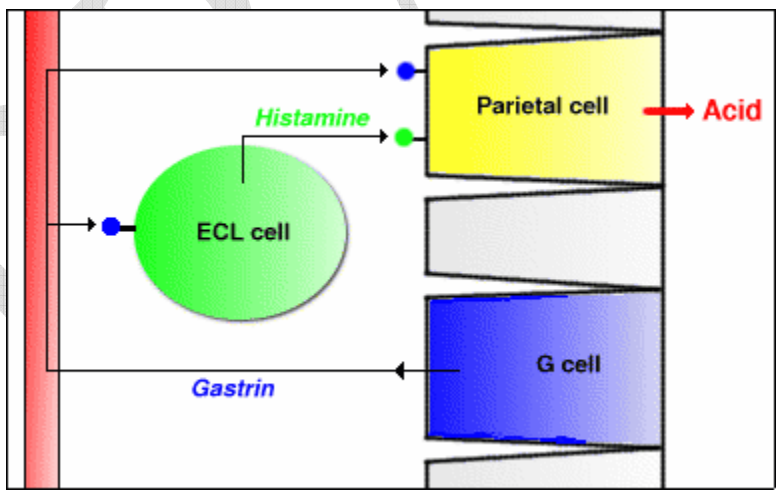
Intrinsic factor is a glycoprotein secreted by parietal (humans) or chief (rodents) cells of the gastric mucosa. In humans, it has an important role in the absorption of vitamin B12 (cobalamin) in the intestine, and failure to produce or utilize intrinsic factor results in the condition pernicious anemia.

Dietary vitamin B_{12} is released from ingested proteins in the stomach through the action of pepsin and acid. It is rapidly bound by one of two vitamin B_{12}-binding proteins that are present in gastric juice; at acid pH, these binding proteins have a greater affinity for the vitamin than does intrinsic factor. In the small intestine, pancreatic proteases digest the binding proteins, releasing vitamin B_{12} which then becomes bound to intrinsic factor. Finally, there are receptors for intrinsic factor on the ileal mucosa which bind the complex, allowing vitamin B_{12} to be absorbed into portal blood.

In all mammals, vitamin B_{12} is necessary for maturation of erythrocytes, and a deficiency of this vitamin leads to development of anemia. Since efficient absorption of vitamin B_{12} in humans depends on intrinsic factor, diseases which decrease the secretion of intrinsic factor (e.g. atrophic gastritis), interfere with cleavage of the binding proteins (e.g. pancreatic exocrine insufficiency) or decrease binding and absorption of the intrinsic factor-vitamin B_{12} complex (e.g. ileal disease or resection) can result in this type of anemia. In cattle and sheep, deficiency in cobalt, which is a necessary component of vitamin B_{12}, can result in anemia among other signs of disease.

Enterochromaffin-Like (ECL) Cells

Enterochromaffin-like or ECL cells are a distinctive type of neuroendocrine cell in the gastric mucosa underlying the epithelium. They are most prevalent in the acid-secreting regions of the stomach.



ECL cells synthesize and secrete histamine in response to stimulation by the hormones gastrin and pituitary adenylyl cyclase-activating peptide. Gastrin itself is secreted by cells in the epithelium of the stomach, but travels to ECL cells via the blood. Together, histamine and gastrin are primary positive regulators of acid secretion from the parietal cell. ECL cells also secrete pancreastatin and probably are the source of one or more other peptide hormones and growth factors. ECL cells are readily identified in histologic sections stained by silver impregnation.

Longer term stimulation of ECL cells by gastrin also stimulates significant proliferation of ECL cells. Such hypertrophy of ECL cells is particularly evident in patients with gastrin-secreting tumors. ECL-origin tumors, or carcinoids, are commonly found in humans and certain rodents. They are clearly associated with hypergastrinemic states and, at least in certain rodent models, are readily induced by long term therapy with drugs that block production of gastric acid.