

Understanding the Human Gut and the Enteric Nervous System (ENS)

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In order to understand food intolerance, it is helpful to understand the gut, its structure (anatomy), and how it works. One problem that makes this more difficult is the use of multiple words for the same thing. For instance, the 'gut' is also the 'gastrointestinal tract', the 'digestive tract' and the 'alimentary tract', the 'oesophagus' is the 'gullet' or 'food pipe', the 'intestine' is the 'bowel', 'faeces' are 'stools' or 'bowel actions' or 'sh**' ! A list of terminology is provided at the back of the book to assist you to understand some important terms.

The main job the gut has is to take in food, break that food down so that energy and nutrients can be extracted, and then expel the remaining waste. This sounds easy, but it really quite a complex process because the gut has to also protect the body from exposure to things that are toxic or not good in other ways for it. The following information is provided to help understand that complexity. There are several websites that show pictorial views of the gut, its parts and its functions and some of these are referenced in the link "Helpful Links, Resources, Research Papers, Studies and Donations" on the www.foodintolerancemanagementplan.com.au website.

The Structure Of The Gut

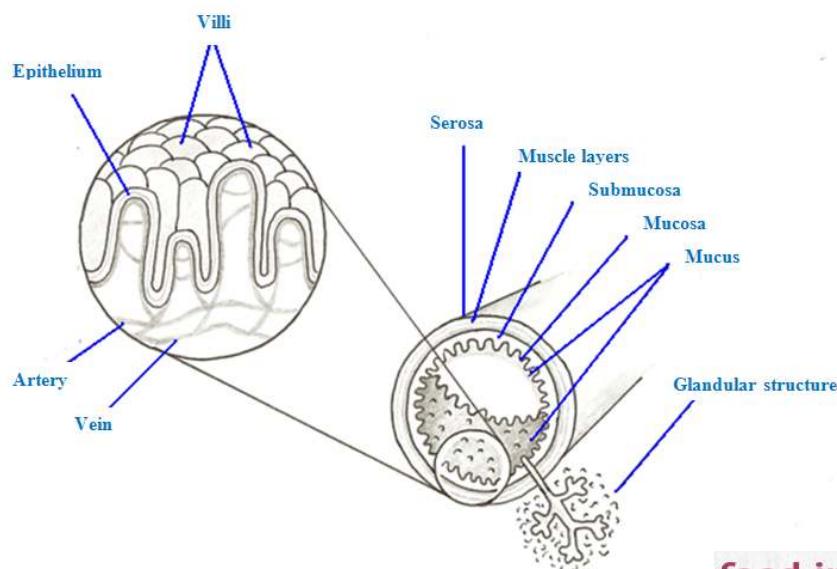
The basic structure of the gut

It is easiest to think of the gut as a hollow tube that runs from the mouth to the anus. As shown in Figure 1 if you slice the tube and look at it end on, you will see that is made up of:

- a *lumen*, which is the central part that holds the cocktail of contents, and
- a *wall*, which has several parts:

- **The mucosa:** This is the lining part of the gut. It has a layer of cells called the epithelium, which acts as the skin of the gut. A layer of mucus (slime) overlies the the epithelium. This acts as a lubricant and helps in protecting the epithelium.
- **The submucosa:** This is the tissue beneath the mucosa through which the blood and lymph vessels brings nutrients and cells to and from the wall.
- **Muscles:** which have an important role to mix and move the contents of the lumen.
- **Nerves:** A complex nervous system called the enteric nervous system (ENS) is embedded within all the layers of the wall of the gut. Its job is to sense what is in the gut and to co-ordinate the muscle movements so that mixing of contents down the gut proceeds in an ordered way,
- **Sources of secretions:** the wall also provides enzymes, secretions and liquids in order to assist in the digestion of food in the lumen. These secretions may come from the cells lining the epithelium, or from specialised glandular structures that are attached to the gut. Some of these structures might be organs in their own right such as the pancreas, the liver and gall bladder, or might just be small glands in the wall of the gut. All these structures have their own passage ways in to the lumen, and these are call ducts (the pancreatic duct, the bile duct).
- **The serosa:** This is a smooth lining of cells on the outside of the tube that is the gut.

FIGURE 1 The basic structure of the gut. It is a hollow tube made up of various layers.



The specialised structures of the gut

The hollow tube that is the gut is made up of many parts in various sections, each performing different specialised functions. The sections have special muscular structures (called sphincters), between them to control what goes through to the next section and to ensure flow is only one way. Because movement of the contents of the gut is generally only in one direction (from the mouth towards the anus), the proper function of any part is somewhat dependent upon the function of the part that precedes it. This will become obvious as each structure is described in the following. The parts are all shown diagrammatically in the picture below (Figure 2). The parts of the gut within the abdomen are very long and stretch for at least 8 metres (25 feet)! How they all pack into the abdominal space is shown in Figure 3.

FIGURE 2 The parts of the gut stretched out. The length of the small intestine and the large intestine is also shown

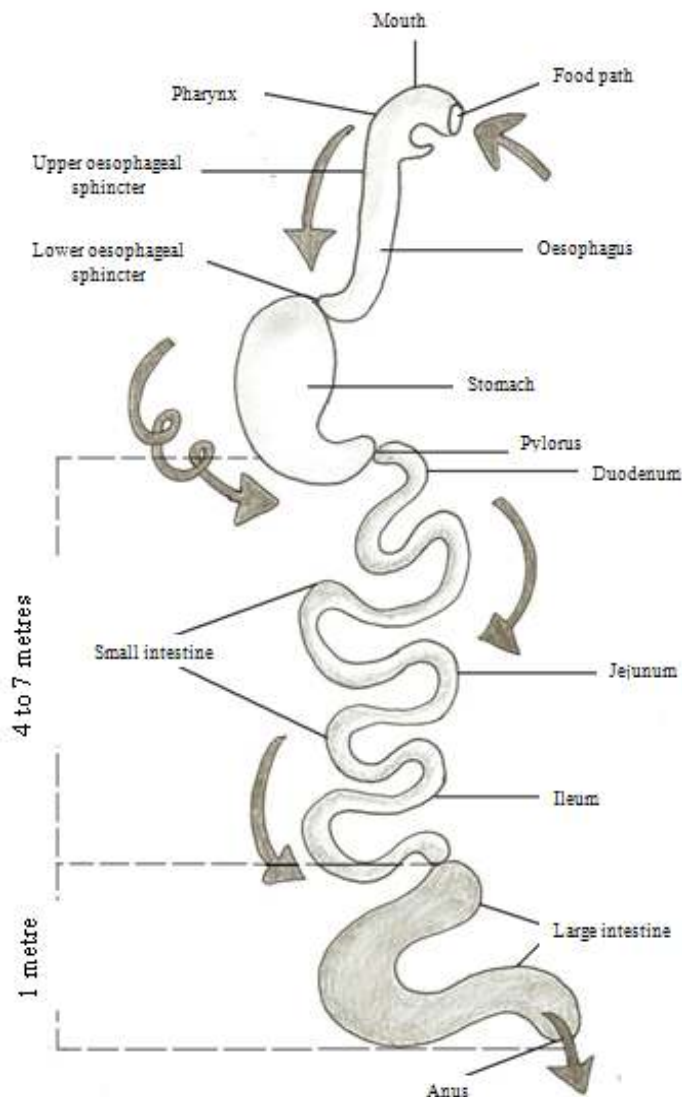
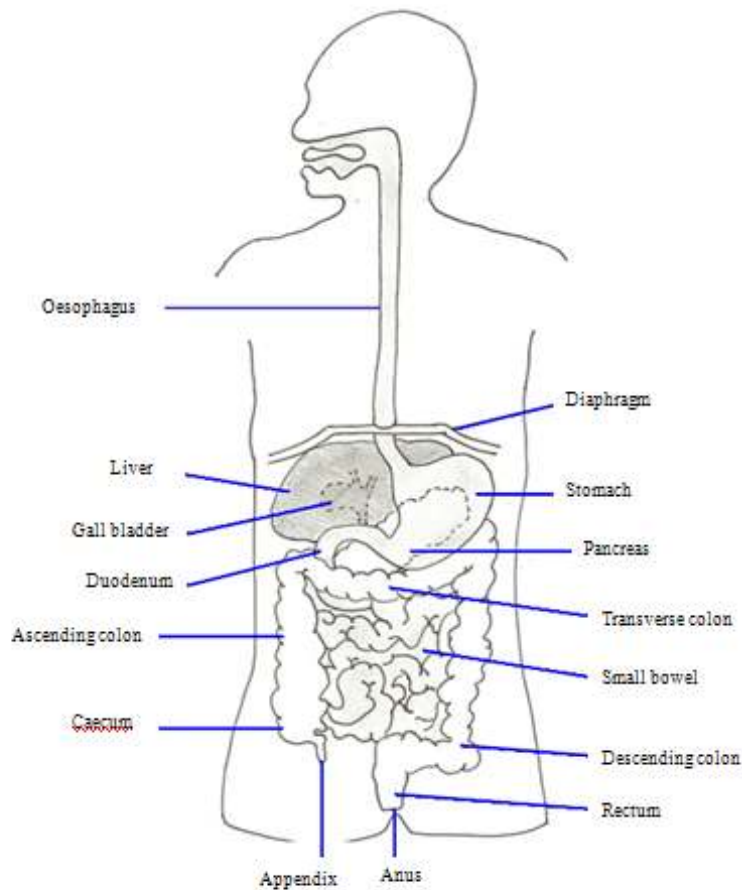


FIGURE 3 How all the parts of gut fit into the body



1. The mouth:

This is the part with which you will be most familiar – food begins its journey of digestion here. There are some highly specialised structures in the mouth that all have important roles. They include tongue, teeth, and salivary glands.

- **Tongue:** the lining (epithelium) of the tongue has lots of taste buds in it that connect to the nervous system of the gut so that it can tell our brain whether the food is salty, sweet, sour or bitter. Most of the tongue is a big muscle that helps move food around the mouth. A chewed mouthful of food is called a bolus.
- **Teeth:** are specialised structures essential for good chewing of food.

- **Salivary glands:** produce liquid that contain enzymes and minerals to make our food moist and to start digestion.

The nervous system of the mouth is very complex and sophisticated! It needs to be, to enable us to swallow – something most of us do without really even thinking about it! The first step is for the tongue to move the food bolus to the back of the mouth (the pharynx) and then to the oesophagus. When the epiglottis (the 'punching bag' that hangs at the back of our mouth) is stimulated by the passing of this food bolus, the upper oesophageal sphincter must relax and the opening to the lungs must close off to prevent food from going down the 'wrong way'.

2. The oesophagus:

The oesophagus is, just as the colloquial term for it, 'food pipe', suggests – is a pipe that takes food from the mouth to the stomach. It does this by co-ordinated muscle movement called peristalsis. We can swallow the contents of the mouth even if standing upside down! Gravity has no part to play in the movement of food down it. Once the food leaves the mouth into the stomach, it should stay there and not reflux back up. The sphincter around the end of the oesophagus (the lower oesophageal sphincter) ensures that travel in the oesophageal lumen is mostly a one-way event. Problems can arise when the muscles do not co-ordinate well because the nervous system of the oesophagus goes 'out of tune'. Occasional reflux of gastric contents does occur, but these are rapidly cleared by peristalsis and this is considered normal. However, conditions such as gastro-oesophageal reflux disease can be caused by excessive reflux of stomach contents (acid).

3. The stomach:

The stomach is a J-shaped pouch that has the important function of storing a big meal and to hold it up while the early processing of food occurs. Its muscular wall is very good at mixing the contents. When the time is right, it permits small amounts of the pulverised semi-liquid contents (known as 'chyme') to be released to the next part of the gut, the first part of the small bowel. This requires the pyloric sphincter to relax. Chewed food that entered the stomach as a semi-solid lump then becomes semi-liquid due to the churning and due to large amounts of liquid being secreted by the stomach lining. This liquid is very acidic, which is important to help breakdown solid

material. Another benefit to being acidic is it reduces the bacterial content of the food (it almost sterilises it). The stomach also secretes enzymes that breakdown proteins.

The length of time that the food contents remain in the stomach varies. Liquids empty from the stomach faster than solids; this makes good sense since there is less to break down. Fatty meals slow down the rate of emptying. Fat content of the meal is sensed by the gut and, hormones are secreted which slow the emptying process down.

When food is in the stomach, it causes the stomach to expand. The expansion is called distension. Distension of the stomach is sensed by the nerves in the stomach. This information is then processed by the nervous system within the gut wall and contributes to the complex process of emptying and mixing the contents. Sensing the distension also leads to messages being sent to the brain. The messages received are a big part of how it is that we 'feel full'. If the stomach empties quickly, you may feel hungry faster. Conversely, if you have a fatty meal, the stomach stays full for longer and keeps you feeling fuller for longer. That is why a meal of 'greasy' fish and chips will keep you satisfied for hours, whereas you will feel hungry again after a large, but low fat salad meal.

What about gas in the stomach? Just about all of the gas in the stomach is swallowed air. We all swallow plenty of air; this occurs every time we swallow a bit of saliva, drinks and food. People tend to swallow more frequently when anxious and, therefore, be likely to swallow more air. The oxygen in the air we swallow can be absorbed across the wall of the stomach and intestine and into the bloodstream. However, the major component of air is nitrogen and this is not absorbed. It has to go somewhere – it can either be belched ('burped') or can be passed out via the anus ('farted'). Some people belch readily – their sphincter at the lower end of the oesophagus is trained to let the gas flow the wrong way. Others seldom belch and the gas then passed into the small intestine. Fizzy drinks of course will introduce a lot of gas quickly and often lead to a large belch, or if belching does not relieve it, gas from fizzy drinks can distend the stomach and/or the small intestine and cause discomfort. This will be explored further later in this document.

4. The small intestine:

The small intestine is a very long tube, being 4-7 metres from the stomach to the colon. It is responsible for converting food into its simple building blocks. It converts carbohydrate into sugars, proteins into amino acids, and fats into fatty acids. It also has a very important role of absorbing all the nutrients including vitamins, minerals, and water present in the food just consumed. The liquid matter passes through the small intestine in only 90 minutes, so it must be very efficient at absorbing all of the building blocks and nutrients. This efficiency depends upon three important things.

- First, food is released from the stomach to the small intestine in a regulated process to ensure excellent mixing and digestion has already occurred.
- Secondly (and most importantly), the small intestine has a huge surface to enable the final thorough digestion and absorption of nutrients. This is possible as the lining looks like a shag-pile carpet, called villi. Each of those piles has itself a shag-pile lining at a microscopic level, called microvilli. It is incredible to think that because of this clever structural design, the surface becomes greater than the area of a tennis court!
- Thirdly, it is separated into three specialised sections - the duodenum, the jejunum and the ileum - which take on specific tasks, as described below.

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- **The duodenum:** This is the first part of the small intestine. Churned and mixed food (chyme) is released from the stomach, into the duodenum which is only about 30 cm long but is a very busy place. It has additional fluids entering it from the pancreas (bicarbonate and enzymes) and from the liver and gall bladder (bile). The digestive juices from the pancreas are alkaline and neutralise the very acidic chyme. This is important to prevent injury of the lining of the duodenum from acid, and to ensure that the digestive enzymes from the pancreas work properly. Bile from the gall bladder and liver is important in the absorption of fats and fat-soluble vitamins. The duodenum must also, therefore, be a good mixer of all the fluids. You can understand why the stomach only releases a certain amount of chyme at a time, so that the volumes are well balanced and mixing is successful. The duodenum prepares the contents for the key absorptive work to be done in the next section of the digestive tract. However, the duodenum is where absorption of folic acid, iron, calcium and zinc occurs.

- **The jejunum:** This is the region that plays the most important part in absorbing the digested products of carbohydrates, fats and proteins, most of the vitamins and minerals, and salts and water. It is about 3 metres in length.
- **The ileum:** Its main role is to absorb salts and water, but it can take on many of the functions of the jejunum if needed (for example, in people who have had surgery removing some jejunum). The ileum has an important task to absorb vitamin B₁₂ (a vitamin important for making blood cells), and bile salts, which are sent back via the blood stream to the liver to be 'recycled'. The other important role of the ileum is in the immune protection of the body; it has the greatest concentration of immune cells of the whole gut and has a key role in 'tasting' what molecules and bacteria that might be in the intestinal lumen. This 'tasting' means the immune system, which is present right along the gut can protect us if any of those molecules or bacteria happen to get too close for comfort, by ensuring the presence of protection and tolerance (see below).

Our intestines contain within them lots of bacteria – this is a normal phenomenon.

The population of bacteria is very small in the duodenum and jejunum, and slowly increases towards the end of the ileum (the terminal ileum). One reason for the low numbers in the small intestine is that there is constant and relatively rapid movement of contents through this region. The only way bacteria can get established in such a 'fast-moving' environment is by sticking to the mucus that lines the epithelium. Bacteria find it easiest to stick to the epithelium of the ileum as the rate of flow reduces there. This is due to the fact in the jejunum that a lot of the water that is gushing down the gut gets absorbed into the blood stream and tissues, so the volume gets less. It makes sense then that the 'tasting area' is located in the terminal ileum. Just next door, in the large bowel, there are vast numbers of bacteria, but the ileocecal valve (the sphincter between the small and large bowel) keeps them in the large bowel. This valve works like a one-way door similar to the pyloric sphincter and the lower oesophageal sphincter as discussed above.

The diseases that affect the small intestine are rather different to all other regions. Cancer is rare. However, food-related illnesses are common since this is the place that luminal contents truly interact with the cells and tissues in the wall of the gut, which is leakier than that in the stomach or large bowel - after all, it has to absorb lots of nutrients. The most common disease is coeliac disease, which arises due to an

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immune reaction to parts of gluten, a protein associated with wheat, rye, oats and barley. Information about diagnosis of coeliac disease is in Chapter One of the *“Food Intolerance Management Plan”*.

5. The large intestine

The large intestine is also called the colon. Although it is only about one metre long, it takes anywhere from 12 hours to 2 days for contents to pass from the beginning to the end of the colon. In many people with constipation, this can be much longer. In other words, what you see in the toilet bowl reflects what you might have eaten a day or two before! The large bowel has an important role as a desiccator. In other words, it changes the 2 litres of fluid entering it each day to neat little packages of ‘poo’ (stools) amounting to 200 ml or less per day. It also deals with waste or undigested food (eg. fibre) in partnership with the vast number of bacteria living on the mucus lining the bowel and in the contents of the large bowel.

Why do we have such a vast number of bacteria in our large bowel? First, there is food galore for them in the bowel. Food that is undigested or indigestible – such as fibre, FODMAPs and some secreted and undigested proteins – is a feast for bacteria, so populations will flourish. Secondly, the large bowel lumen is not a ‘rapidly-moving’ environment. It might help to think of the progress as the contents take a few steps forward and occasional steps back with resultant slow progression towards the anus (as discussed above). There is plenty of time for the bacteria to multiply.

You only have to look at and have a smell of the excreted contents of the large bowel (a ‘poo’) to wonder how can they be anything but toxic or bad for you in the bowel? The truth of the matter is that our large bowel bacteria live in a harmonious relationship with us; that is, they benefit from being there and we benefit from them being there. They are our friends. We feed them with carbohydrates and proteins, and provide surfaces for them to grow happily and keep out of trouble, while they help process our waste, produce energy and important fuels for our bowel to be healthy, assist in the desiccation process, and protect us from nasty (pathogenic) bacteria (that can cause disease). They also provide bulk in our faeces – much of a well formed bowel motion is bacterial mass! If you consume a diet that does not feed the bacteria (e.g., a very low fibre diet), the bowel motions will become dry, small in quantity and hard to pass.

The bacteria help by more than just the bulk-producing effects. They process and breakdown carbohydrates by fermentation. Like other fermentation (beer and wine production, bread-making), gas is produced. This is mostly hydrogen, carbon dioxide and, in some of us, methane. This will be discussed at length later. The other products of fermentation of carbohydrates are short-chain fatty acids. One of these, butyrate, is the major fuel for the epithelial cells to produce energy and survive. Butyrate also protects the cells from cancerous change. This is one reason why a diet high in fibre probably reduces our risk of bowel cancer – fibre is a major source of butyrate production and increasing its intake will increase the amount of butyrate produced. In order to grow, bacteria need nitrogen to make proteins as part of their own structure. Bacteria obtain nitrogen from 1) proteins that might not be digested or are part of the body's secretions, and importantly 2) from ammonia and phenols, which are chemical compounds produced from metabolic processes in the body. Scientific evidence suggests it is not good to have high levels of ammonia and phenols in the bowel as they promote cancer development. The bacteria once again do us a favour by removing these products and making the contents safer. If the bacteria are given too much protein to ferment, they will make gases including hydrogen sulphide (also known as rotten egg gas), which is why some wind/flatulence can be smelly – a minor side effect of some excellent work!

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One of the most fascinating aspects to bacteria in the bowel is that the range of bacteria we have is fairly constant over time in each person, and no two people have the same range. Even if you take antibiotics that can change the bacteria, or flush them out with a severe colonic wash-out (called a 'colonic purge'), the bacterial populations will recover and return to their usual range. How it is that is the case is only partly understood, but the range of bacteria is established early in life. This can be likened to a 'Club Membership' being created early in life and new members are not allowed! A large amount of interest surrounds the idea that some people have a poor balance of 'good' and 'bad' bacteria and this then causes illnesses such as irritable bowel syndrome, or makes illnesses such as inflammatory bowel disease harder to fix. Trying to change the 'membership' has proven to be difficult. One strategy is by taking bacteria that may have health-promoting benefits, called probiotics. However these will only gain 'temporary Membership' and will only stay present if the 'probiotic' continues to be taken. We can also take 'prebiotics', which are specific carbohydrates that are the food preferred by the 'good' bacteria. Therefore, consuming 'prebiotic' molecules usually increase the number of good

bacteria who are already members (and they also dilute out the less welcome 'bad' members). While all this theory is great, proof that the changes in bacteria are indeed beneficial for specific circumstances like irritable bowel syndrome is needed. This will be discussed later in this document.

The large bowel has different regions with specialised functions. Refer to Picture? figure 3 to see a picture of these.

- The *appendix*, is a worm-like structure that is attached to the first part of the large intestine (called the caecum). It is probably important for developing immune defence in the large bowel. However, we seem to get along perfectly well if it is removed.
- The *caecum*, ascending colon and transverse colon are all very important in the drying out of the faecal contents.
- The *descending colon*, which is much narrower, and the *sigmoid colon* (so named because of its 'S' shape) really just serve as storage containers for the waste products ready to be expelled (although they do continue the drying out process).
- The *rectum* is the last part before the outside and it is not that keen on being full. It senses the distension and notifies us of the case by sending messages to the brain that you should visit a toilet. If the contents are liquid, it becomes very impatient and you must attend to it urgently (this is called 'urgency').
- The *anus* is the opening from which the faeces is excreted from the rectum to outside the body. The sphincters (specialised muscles) of the anus prevents the contents of the rectum from being released automatically. The 'external sphincter' is under conscious control while the 'internal sphincter' is not. Normally, the external sphincter can be considered the 'master controller'. However, if this is damaged (for instance at child birth), the control may not be as good and incontinence can sometimes occur. The other reason for incontinence is when the contents are so liquid that the unconscious mechanism for defaecation overrides the conscious.

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The Relationship Between The Body And Gut

Contents

The body and the contents of the gut are like a marriage – a harmonious, mutually beneficial relationship, with the potential for small episodes of disharmony and very occasional all out war!

The human body is a carefully controlled environment. The temperature, water content, acidity, concentration of salts, sugar levels in the blood, and so on are controlled within very strict limits. If that control fails, bodily function is disturbed and illness can occur. This carefully controlled internal environment is a contrast to the outside environment, where we have only limited control to what we are exposed. We all understand that our skin is an important interface between the outside world and our body's internal environment. The skin is relatively impermeable due to its thickness and coating of keratin. If this is broken or badly damaged, it becomes the site at which infection can enter the body.

In the same way, the lumen of the gut is the outside world and the gut's lining is the interface between it and the carefully controlled environment of the body beneath. Compared with the skin, the lining of the gut is thin and must extract things (such as nutrients) from the lumen. This opens the way for environmental toxins or other potentially harmful things to reach the body's tightly controlled environment. Likewise, proteins and other substances can leak into the lumen if the lining of the gut is not working properly. Under the very thin skin of the gut lay complex protective mechanisms that are a major part of our immune system. This system is incredibly effective system in that it is able to protect us from exposure to a huge array of potentially harmful molecules.

How does our gut manage to live happily with the faeces and bacterial contents of the lumen? First, each section of the gut is designed to cope with its local area conditions. The oesophagus has a relatively tough lining and gets things to travel through it very quickly. The stomach's lining is able to effectively protect itself from the very acidic environment it creates via its secretions. The small intestine can quickly neutralise the acid, has a huge surface area and somewhat permeable (leaky) lining to allow rapid absorption of nutrients to occur since it moves its contents quickly along so that bacteria do not have much of a chance of staying around to

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cause trouble. The large bowel has a very tight, non-leaky lining as things sit in it for many hours, and it therefore has a very different and mutually beneficial relationship (a 'happy marriage'!) with the bacteria that live there (as outlined above).

Secondly, the immune system in the wall of the gut learns what is normally present in the lumen and develops protective systems. One example is that the immune system 'tastes' what is in the environment and then develops antibodies against those things. The cells that produce these antibodies then get sent to many areas of the gut where, with the co-operation of the epithelial cells, the antibodies make their way to the mucus layer. Here, they can neutralise proteins or bacteria that get too close for comfort before they make it to the epithelium itself. The immune system also develops 'tolerance' to microbes and molecules. If they get too close or are able to penetrate the barrier, the immune system deals with them quietly without getting excited.

Fortunately, most symptoms deriving from the gut are not due to the immune system reacting to contents of the gut. Food allergy and food hypersensitivity, where there is an immune reaction to food with subsequent development of gut and other symptoms, is fortunately very uncommon (see later discussion specifically on this). The symptoms are more related to the gut's personality!

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The enteric nervous system (ENS): it's all about personality

As human beings, we are all different. One person might be a fun-loving, talkative person, the next a quiet, serious person and another a worrier who sleeps poorly. This we all understand and accept.

But why are we so different? It is an interaction of the individual's personality and influences from outside the brain – from the environment and from the rest of the body. We develop our personality during the early years of life and it forms the 'core' or baseline from which our reactions to external influences are formed. For example, how one individual reacts to illness can vary from a positive to negative outlook, from coping with the symptoms of the illness to becoming sullen and angry. If major life stress occurs, an individual can react by becoming introverted or depressed, while others might become angry and aggressive. How a person reacts, i.e., their

behaviour and personality, is a consequence of baseline personality and how it responds to all those external influences.

The gut is no different! The gut has its own personality that resides in the gut's own brain, which is better known as the 'enteric nervous system' ('ENS'). Ultimately, how our gut works (whether it behaves or misbehaves) is a blend of baseline personality of the gut and how it responds to all of the external influences on the ENS. In order to understand why symptoms develop and how the gut's personality expresses itself, we need to know a bit about how the ENS works (and doesn't work).

As described in the discussion above regarding the structure of the gut, there is a complex nervous system in the gut that stretches from top to bottom and is present in all those layers in the wall of the gut. A diagram of it is shown in **Picture?Figure 2**. The ENS senses what is going in the gut and controls the motility (ie, muscle activity and its coordination). It has its own memory and takes part in many reflex actions. It is connected to the brain via the autonomic nervous system, but the ENS can function without these connections. Like the brain, function of the ENS involves networks of neurons (nerves). When a neuron is stimulated, it sends electrical signals down its long fibre to the other end of that neuron. The electrical signal is communicated to other neurones via releasing neurotransmitters, chemicals released from the end of the nerve (serotonin is an example). These then stimulate or inhibit the start of other neurons by binding to special receptors on their surface (like a key fitting a lock). The neurotransmitter locking into a specific receptor can shut down (inhibit) that neuron or excite (stimulate) it. Excitation will then lead to electrical impulses passing down its long fibre-like body to the end where it will either similarly communicate with other neurons or with muscle fibres to make them contract. This is made more complex by the fact that there are many different neurotransmitters all with their own specific receptors, and that there are many different receptors that will permit the same neurotransmitter to lock into it. Needless to say, different receptors will have different effects even when the same neurotransmitter is released. This then is a complex network of fibres, nerve endings, neurotransmitters and receptors that somehow retains memory and co-ordinates the complex activities of the muscles of the gut.

The way that the ENS senses things and drives the muscles of the gut is due to the unique relationships between neurons, neurotransmitters and receptors in an individual – no two people will be alike. We all have different spectrum of

neurotransmitters and receptors. Some of this is dictated by our genes; for example, some of us have genes which tell us in our development to produce lots of a certain type of neurotransmitter whereas others might only produce a small amount. How our bowels then perform will be determined by how this complex system is tuned. No wonder we know so little about how to re-tune it when it is not tuned to our liking!

The ENS does not work in isolation. It can be influenced by neurons from the brain and spinal cord, which will communicate with the neurons of the ENS in the same way (ie, via release of neurotransmitters when the nerves are excited). Other cells that lie close by to the nerve endings may also release chemicals that can affect neurons. An example is the mast cell, which contains lots of granules full of substances, such as histamine, that can interact with the nerve fibres. When we are allergic to something, mast cells are told to release their granules, and the histamine can then affect the nerves and the muscles to make them contract. If this happens in the bronchi (the tubes taking air to the lungs), muscles in the walls of the bronchi contract, obstructing the flow of air. This we call asthma. Likewise, such a reaction occurring in the intestine can cause diarrhoea or abdominal pain.

It is not unusual for drugs or medication we take to cause diarrhoea or constipation. One way they can do this is via effects on the ENS. A very good example is codeine, a pain reliever that almost always causes constipation. Codeine binds to receptors that block muscle movements in the bowel. It is not difficult then to understand how constipation will be caused by the use of codeine.

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In our diet, we may consume many substances that might contain small chemicals (naturally or introduced by humans). We also break down many big molecules to small chemicals in the process of digestion. Bacteria also break down many substances in our diet (this is a normal and healthy process), but some of these substances may be chemicals that can influence the neurons of the ENS. Therefore, in the lumen of the intestine, we have many substances that might influence how our ENS performs. Fortunately, we have very efficient ways of dealing with these substances so that they find it hard to get near our neurons. Some, however, do. Thus, they potentially may affect how the ENS performs. For example, they can:

- change the how sensitive the nerve fibres are in the bowel, so they have a lower threshold and react quickly to sensation (called visceral hypersensitivity); or
- lead to the release of chemicals from cells like mast cells; or

- interact with the receptors on the neurons to cause changes in how they get excited.

How do we know what is going on in the abdomen?

For the ENS to work well, it needs 'sensory input'; that is, it needs information about what is happening in the gut. This is achieved by having sensory receptors on specialised (sensory) neurons whose job is to detect activity that is of relevance to the function of the gut. The situation in the gut is very different to that in other parts of the body. Take your hand as an example. In the hand, you have sensory neurons that can detect fine touch, sharpness and temperature. This makes good sense since as being gently touched on the hand by a loved one is a pleasant sensation that is encouraged. In contrast, touching something very hot can cause injury and we can quickly move the hand away from such stimuli, protecting us from injuring the hand.

What sensations are important in the gut? It is not particularly useful for the ENS to know about fine touch or even temperature since, for example, hot things being put into the gut have already been 'screened' as it enters the mouth. It is known that taking pinch biopsies of the lining of the gut at colonoscopy is not sensed either by the ENS or by the brain. In other words, a person having a biopsy is not aware that the pinch biopsy is occurring. What is very important in the gut, however, is its *distension*. The ENS has stretch receptors to detect this. So, for example, when the stomach is distended by food, the ENS directs the muscles at the outlet to the stomach to relax and the muscles in the body of the stomach to contract so that there is a controlled release of the contents of the stomach into the intestine. Similarly, distension of the large bowel leads to the ENS directing the muscles in the wall of the large bowel to contract in such a way that the contents are moved towards the anus. This is called peristalsis. If the bowel is rapidly distended with lots of liquid, it hurries the content through the bowel, not allowing time to desiccate the contents...this is how diarrhoea is the output, instead of the usual packages of formed stools that are usually released at one's leisure.

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To know what is going on in the gut, the brain must get information from the ENS. However the sensory information that is rapidly processed by the ENS is also sent to the spinal cord, where further processing goes on. Information is then sent to the brain, but it can be processed in a few areas on its way. In other words, the message that finally gets to the conscious brain will be influenced at several levels.

How can the brain influence the gut?

We do not have conscious control over how the ENS works. For instance, we cannot tell the stomach to empty its contents. Likewise, if the ENS decides that the stomach must empty its contents the wrong way (that is, vomit), we cannot consciously stop this. However, when we are asleep, the gut becomes very quiet in its activity and this is at least partly due to the effect of messages from the brain to the ENS. In contrast, when we are very anxious, the brain's output via the sympathetic nervous system can make the ENS 'anxious' and activity can increase (for example, diarrhoea might occur like before a major examination or an important football match). In other words, the brain can influence both our perception of what is happening in the gut and also the activity or tuning of the ENS.

The best way of understanding how the brain and ENS interact is to discuss specific examples of that interaction. The normal way we learn of the need to open our bowels (ie. feel the need to 'go to the toilet') is that the brain is told that the rectum and sigmoid colon are full and ready for emptying. The brain then will direct the individual to go to the toilet, to get into position and to relax the muscles under brain's control in the pelvic floor (around the anus). The ENS can ensure that the contents ('poo') are pushed by the muscles under its control through the anus to the exterior of the body. If the ENS is particularly stimulated by, for example, a large amount of very liquid contents, the brain might not get a warning early enough to ensure defaecation ('pooping') is ordered and controlled, so the individual might soil themselves (be incontinent).

The sensation of bloating is another good example. How does the brain know that the abdomen at least feels distended and uncomfortable? Sensory nerves detect that the gut is distended (could be the small intestine, the large bowel or the stomach). These sensory neurons are excited and the message they send is processed through the ENS to reach the spinal cord and this message is then sent up to the brain. Some people might feel mildly uncomfortable, while others might feel actual pain. This will depend upon how much excitement gets sent by the nerves to the brain receiving the message. Where the information ends up in the brain depends in part on the size of the signal and in part the function of the brain itself. If this signal occurs whilst someone is busy doing some other activity, such as playing a football match, the brain will choose to ignore the signal. However, in a tired person in the quiet at the

end of the day, the brain might direct the signal to the pain centre itself and this person, who isn't distracted by any other activity, they will experience significant discomfort. Also, one person might look obviously distended (stomach 'sticking out') with this sensation of bloating, whilst another person might not be visibly distended but can still experiencing very uncomfortable bloating feelings. The main explanation for this is that this person has visceral hypersensitivity – a *small* distension of the gut leads to great excitation of sensory neurons and a *big* signal going to the brain. In other words, the threshold by which the latter person's ENS tells the brain that the gut is distended is much lower than that of the former person. This concept has indeed been observed in carefully designed research studies.

The implications of this complex interaction between the brain and the ENS are important. How readily the conscious part of the brain knows about what is happening in the gut will depend upon the tuning the ENS – i.e., its sensitivity to distension or other stimuli (visceral hypersensitivity will make it more sensitive) – and how the signals are processed by the brain which will be dictated by multiple factors including the state of mind, the environment, the presence/absence of distractions, past experiences and how the brain is itself tuned.

Can the ENS be re-tuned?

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The answer is yes. In some people, after a nasty gastroenteritis, the ENS is re-tuned to make things travel through it rapidly with resultant diarrhoea. This is called post-infectious irritable bowel syndrome (IBS). How this re-tuning occurs is not well understood but presumably relates to some damage to the ENS from the infection itself. Also, it is well known that some people develop IBS in their twenties after having a normal and untroubled functioning gut without any apparent severe gut illness. These are examples of where the ENS has been re-tuned to be *disturbed*. One explanation that is often suggested is that it is in the brain where the problem lies (a 'psychosomatic' problem). Such an explanation doesn't add up though, since the sensory stimulation of the brain is an essential part of perceiving things are not right in the abdomen. These stimuli would rarely originate in the brain.

An important question for anyone who has a disturbed ENS and wants it re-tuned is whether the person themselves or health professionals can therapeutically re-tune to *improve* the ENS. The answer is unfortunately no at the present time. Drugs that change the nature of the neurotransmitters or can block or stimulate certain receptors

on the neurons have had very limited success and some have been associated with rare side effects that have restricted their use or led to their withdrawal from the market. There is some evidence that psychological therapies or hypnotherapy might alter the ENS, but this is not proven and how they might do that is not known. If we understood how ENS dysfunction occurs in the first place, then we might be heading towards the real 'cure' for IBS.

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