INTRODUCTION
Diarrhoea is one of the commonest presenting complaints seen in small animal practice and is associated with a large number of differential diagnoses. This paper will review the underlying pathophysiology of diarrhoea, an understanding of which will assist the clinician when investigating individual cases and their subsequent treatment.

ANATOMY AND PHYSIOLOGY OF THE INTESTINE
The alimentary tract in the dog and cat is composed of five different layers throughout its entire length (Fig. 1). Although the serosa, muscle layers (longitudinal and circular) and submucosa are consistent throughout the tract, the mucosa differs significantly in its construction between the small and large intestine. This difference reflects the differences in function between the two regions: namely digestion and absorption of nutrients primarily occurs in the small intestine while the large intestine’s role is the absorption of water and electrolyte from faecal material.

Small intestine
The small intestine in the dog and cat is relatively short and if the mucosa was simply a smooth surface this would provide an inadequate surface area for...
efficient digestion and absorption of nutrients. In order to increase the surface area for these functions the mucosa of the small intestine is thrown into longitudinal folds (Fig. 2). This increases the surface area approximately ten times. Further increases in surface area are achieved by development of the main functional unit of the small intestine called the villus (Fig. 3). These finger-like projections increase the surface area for absorption of nutrients by a further ten times. Each villus is lined by mucosal cells called enterocytes, which are produced by rapidly dividing cells at the base of each villus called the Crypts of Lieberkuhns. As the enterocytes migrate up the villus they mature into functional absorptive cells before being shed into the lumen. On the luminal surface of each enterocyte are hair-like processes called microvilli which carry brush border enzymes for the final stages of digestion and membrane carriers for the absorption of the main nutrients. The continual production of new enterocytes results in the mucosal surface being renewed every three to four days throughout life. The crypt cells have one other function, being responsible for the majority of secretion into the small intestinal lumen.

Understanding the role of the villus has special importance in understanding the pathophysiology of diarrhoea as virus infections such as coronavirus and rotavirus target the mature enterocytes and interfere with absorption of nutrients and fluid, resulting in an osmotic diarrhoea. This infection is short-lived as crypt cells rapidly replace those enterocytes damaged by the virus. However in the case of parvovirus both mature enterocytes and crypt cells are destroyed resulting in more severe and longer lasting damage which can lead to loss of the mucosal barrier and translocation of pathogens. Bacterial pathogens act by producing toxins which stimulate fluid secretion by the crypt cells. The net result being excessive secretion of fluid and electrolytes into the lumen, called secretory diarrhoea.

Within each villus is a rich capillary network which assists in the transport of nutrients from the enterocytes to the portal vein for transport to the liver. Also present in the villi is a single blind ended lymphatic vessel called a lacteal, which is responsible for the transport of fat and fat soluble nutrients from the enterocytes into the lymphatic system and ultimately the circulation.

Large intestine

The mucosa of the large intestine or colon is arranged differently to that of the small intestine, reflecting a different function. The mucosal cells of the large intestine are called colonocytes and although there are crypts where new cells are produced, there are no villi or microvilli as seen in the small intestine. Between the colonocytes are numerous goblet cells responsible for mucus production. The colonocytes are primarily responsible for the reabsorption of water and sodium chloride from the faeces prior to their storage in the rectum. The colon can absorb up to 90% of the water presented to it and has a large functional reserve to ensure that even when excessive fluid reaches the colon from the small intestine, ‘formed’ faeces can still be produced. However damage to the colonocytes or interference in their function can seriously disturb this function resulting in diarrhoea.

Intestinal permeability

The intestine acts as an effective barrier to translocation of organisms and macronutrients. Macronutrients and non-sterile antigens are prevented from entering the circulation by tight junction proteins which bind enterocytes together (Fig. 4). The permeability of the tight junctions varies along the intestinal tract. Where permeability is high micronutrients, particularly electrolytes and water can pass between tight junctions. Permeability between tight junctions is greatest in the duodenum while the colon is largely impermeable to sodium and water movement. It is essential that the colon is impermeable to the passive movement of fluid across tight junctions to allow the formation of firm faeces. Steroids, bile acids, hydroxy fatty acids and bacterial toxins can damage the tight junctions leading to increased intestinal permeability.

Fluid movement

The contents of the intestinal tract are hypertonic and this hypertonicity increases as larger molecules are digested and broken into smaller molecules (e.g. proteins are broken into small peptides and amino acids). Due to this large osmotic gradient there is a tendency to draw water into the lumen by passive diffusion predominantly through tight junctions between cells. As permeability decreases along the intestinal tract less water is able to move through tight junctions and into the lumen.

Apart from hypertonicity, multiple other active and passive transport mechanisms are present in the intestinal tract and are important in the regulation of fluid and electrolyte movement. Fluid balance is largely controlled by neuroendocrine systems. Acetylcholine and vasoactive intestinal peptide (VIP) are the main neurotransmitters that stimulate secretion by enterocytes (crypt cells) in the small and
large intestine. These stimulatory neurotransmitters result in increased cytosolic calcium either by increasing calcium influx into the cell or release of calcium from intracellular stores. Increased cytosolic calcium results in increased production of prostaglandins and among other effects prostaglandin causes increased production of cyclic adenosine monophosphate (cAMP). Increased cytosolic calcium, prostaglandins and cAMP in general reduce absorption of sodium and chloride and increase chloride and potassium secretion into the intestinal lumen. Increases in luminal sodium concentrations result in passive movement of water into the lumen. Noradrenaline, somatostatin and opioids cause increased absorption of water by lowering intracellular cAMP concentrations and stimulating sodium and chloride absorption.

As permeability between tight junctions decreases in the distal intestine the active process of water absorption increases, being greatest in the colon. In a normal animal this results in a net gain of water and the formation of ‘formed’ faeces. Absorption is an energy dependent process that is coupled to the movement of sodium and non-electrolyte solutes across the mucosal barrier. In a healthy animal approximately 50% of the daily fluid intake (including salivary, gastric, pancreatic, hepatic and intestinal secretions) is absorbed in the duodenum and jejunum, 37% in the ileum and 12% in the colon. In the jejunum movement of sodium is coupled to the absorption of glucose and amino acids. In the ileum and colon sodium absorption is not coupled to the movement of other solutes. In the colon sodium absorption occurs across an electrochemical gradient with sodium moving from a high concentration in the lumen to a low concentration inside the epithelial cell. The electrochemical gradient is created by sodium-potassium ATPase pumps that transport sodium into the cells and eventually the interstitium. Glucocorticoids and aldosterone are important stimulants of this system.

**Enteric nervous system**

The enteric nervous system consists of the myenteric and Meissner plexus. The myenteric plexus is located between the circular and longitudinal muscle layers, the Meissner plexus lies in the submucosa. Gastrointestinal motility is mainly controlled by the myenteric plexus while the Meissner plexus controls gastrointestinal secretions and local blood flow. Most of the stimulatory or excitatory neurones are cholinergic with the main neurotransmitter being acetylcholine although many other local transmitters are present (eg 5-HT). Acetylcholine inhibitors such as atropine or hyosine have a profound effect on the myenteric plexus and result in a significant reduction in smooth muscle contraction in the intestinal tract. Parasympathetic and sympathetic neurones link the enteric nervous system to the central nervous system. Innervation via the vagus nerve (parasympathetic) has a high degree of control over intestinal motility.

Contraction of the longitudinal smooth muscle results in peristalsis and aboral movement of ingesta. Contraction of the circular smooth muscle results in segmentation (Fig. 5) which has several important functions:

- creates no movement of chyme along the intestine
- mixes chyme with digestive enzymes and bile acids
- aids the efficient breakdown of nutrients
- aids the efficient absorption of nutrients by enterocytes.

**Microflora**

The intestinal tract is not a sterile environment and normally contains a resident population of bacteria. The intestinal microflora is an important part of the digestive system being involved in micronutrient digestion, stimulation and development of the enteric immune system and helps in protection against invasion by pathogenic micro-organisms. In general the number of bacteria increases from the duodenum to the colon, gram positive organisms...
predominate in the small intestine and anaerobes in the large intestine. Non pathogenic bacteria adhere to the mucosal surface and form an important part of the mucosal barrier which prevents the adherence and invasion of pathogenic bacteria. Most pathogenic bacteria have to displace the normal non pathogenic flora before they can bind to the mucosa and cause disease. The small intestinal microflora influences factors such as villus height, turnover of enterocytes and brush border enzymes and intestinal motility. The bacteria also affect digestion and assimilation of fats, carbohydrates, proteins, amino acids and vitamins. The colonic microflora can metabolise carbohydrates (largely fibre), proteins and lipids. Of most importance is the metabolism of fibre to produce short chain fatty acids (SCFAs), predominantly acetate, propionate, and butyrate. These SCFAs are essential for provision of colonocyte nutrition. Butyrate is the primary source of energy for colonocytes and is important for colonocyte growth, maturation and repair.

**CLASSIFICATION OF DIARRHOEA**

Diarrhoea may be defined as faeces with an increase in the fluid or nutrient content. It may be further defined based on duration of clinical signs as either acute or chronic. With a knowledge of the differing functions of the small and large intestine it may be possible from the history to further classify the diarrhoea as primarily small intestinal, large intestinal or mixed (diffuse) disease (Table 1). An alternative approach would be to classify the diarrhoea according to its pathophysiology as osmotic, secretory, abnormal mucosal permeability or abnormal motility (Table 2).

**Osmotic diarrhoea**

Osmotic diarrhoea is generally associated with disorders of maldigestion or malabsorption which results in an increase in the number of osmotically active particles in the lumen. Excess osmotically active particles retained within the intestinal lumen result in an osmotic retention of water in excess of the absorptive capacities of the small and large intestine. A feature of osmotic diarrhoea is that it generally resolves with fasting the patient. Good examples of maldigestion and malabsorption, resulting in osmotic diarrhoea, include exocrine pancreatic insufficiency and inflammatory bowel disease although there are a range of other causes.

---

**TABLE 1: Differentiation of small and large intestinal diarrhoea**

|                          | Small intestinal diarrhoea | Large intestinal diarrhoea |
|--------------------------|----------------------------|----------------------------|
| **Frequency**            | Mild increase (<3x/day)    | Markedly increased (>3x/day) |
| **Faecal volume**        | Increased                  | Decreased                  |
| **Urgency**              | Usually absent             | Often present              |
| **Tenesmus**             | Rare                       | Common                     |
| **Faecal mucus**         | Rare                       | Common                     |
| **Fresh blood**          | Rare                       | Common                     |
| **Melaena**              | May be present             | Rare                       |
| **Dyschezia**            | Absent                     | May be present             |
| **Flatus/borborygm**     | May be present             | Usually absent             |
| **Vomiting**             | May be present             | May be present             |
| **Weight loss**          | Common                     | Rare                       |

**TABLE 2: Classification of diarrhoea**

| **Anatomical location** | Small intestine | Large intestine | Mixed (diffuse) |
|-------------------------|-----------------|-----------------|-----------------|
| **Time period and severity** | Acute, non-fatal, self limiting | Acute potentially fatal | Chronic |
| **Physiological basis** | Osmotic         | Secretory (abnormal water and electrolyte transportation) | Abnormal mucosal permeability | Motility disorders |
| **Aetiological basis** | Allergic        | Inflammatory    | Neoplastic      | Extra-intestinal (e.g. EPI, liver disease) | Infectious (viral/bacterial/parasitic) |
Osmotic diarrhoea is probably the most common cause of diarrhoea in cats and dogs. Secretory diarrhoea occurs when stimulation of crypt enterocytes causes release of excessive levels of fluid and electrolytes into the intestinal lumen. In the small intestine toxins released by pathogenic bacteria (e.g. *Clostridium perfringens*, *Campylobacter* spp, *Salmonella typhimurium*) often cause diarrhoea as a result of increased intracellular cAMP leading to increased secretory activity. Unabsorbed bile acids or hydroxy fatty acids can stimulate secretion of fluid in the colon. The absorptive capacity of the small and large intestine is generally retained in secretory diarrhoea but secretion is in excess of this absorptive capacity. Secretory diarrhoea does not generally resolve with fasting and severe fluid loss can occur resulting in dehydration.

Abnormal mucosal permeability

In health tight junctions between enterocytes closely regulate movement of solutes across the mucosa. Inflammatory, infiltrative or ulcerative diseases or portal hypertension can disrupt mucosal integrity resulting in leakage of fluid into the intestinal lumen. In severe cases protein will be lost resulting in protein losing enteropathy.

Motility disorders

True hypermotility as a cause of diarrhoea is rare in cats and dogs. The best example of a hypermotility disorder is feline hyperthyroidism. Hypomotility is the most common abnormality associated with diarrhoea and is primarily the result of reduced segmental contractions causing decreased exposure of nutrients to the digestive and absorptive capacities of the mucosal surface. The increased volume of luminal contents stimulates peristaltic motility resulting in the impression of hypermotility and urgency. Any process which results in inflammation of the intestine is likely to alter normal motility patterns. Examples would include inflammatory bowel disease, colitis, and viral enteritis. Irritable bowel syndrome is associated with disorganised intestinal motility, either hypermotility or hypomotility.

**TABLE 3: Causes of diarrhoea**

| Category                      | Causes                                                                 |
|-------------------------------|------------------------------------------------------------------------|
| Osmotic                       | Sudden change in diet, Scavenging, Over eating, Malabsorption (e.g. IBD, intestinal lymphoma, lymphangiectasia, portal hypertension) |
| Secretory                     | Pathogenic bacterial toxins (e.g. toxins produced by *Clostridium perfringens*, *Campylobacter* spp, *Salmonella typhimurium*), Unconjugated bile acids from bacterial fermentation, Hydroxylated fatty acids from bacterial fermentation, Giardiasis |
| Abnormal mucosal permeability | GI ulceration (e.g. secondary to NSAIDs), Inflammation, Infiltration (neoplasia), Lymphangiectasia, Portal hypertension |
| Abnormal motility             | Sudden change in diet, Scavenging, Irritable bowel syndrome, Feline hyperthyroidism, Secondary motility disorders (often ileus is present) • Inflammation • Ischaemia • Infection (viral/bacterial) • Anticholinergic drugs • Abdominal surgery • Peritonitis • Pancreatitis |

Key: EPI: exocrine pancreatic insufficiency, IBD: inflammatory bowel disease
Mixed disorders
Although useful in providing an understanding of the cause of the diarrhoea it must be remembered that the above mechanisms of diarrhoea do not usually occur in isolation. For example inflammation of the intestinal tract may result in abnormal motility, poor absorption and alteration of epithelial permeability, all of which result in a greater osmotic load being presented to the colon and ultimately diarrhoea.

SUMMARY
A thorough history and physical examination of every patient with diarrhoea is required in order to classify the type of diarrhoea that is present. This is extremely important in creating a list of the most likely differential diagnoses. In the case of acute, non-life threatening, self limiting diarrhoea where further extensive investigation of the exact aetiology may not be warranted, classifying the type of diarrhoea is useful in guiding the appropriate choice of symptomatic treatment. In chronic diarrhoea patients classifying the type of diarrhoea which is present helps determine which diagnostic tests are likely to provide a definitive diagnosis and thus allow provision of specific therapy.

REFERENCES AND FURTHER READING
JONES, S. L. BLIKSLAGER, A. T. (2002) Role of the Enteric Nervous System in the Pathophysiology of Secretory Diarrhoea JVIM;16:222-228.
BSAVA Manual of Canine and Feline Gastroenterology 2nd Edition: Editors Hall, E. J. Simpson, J. W. Williams, D. A.
Small Animal Clinical Pharmacology: Editors Maddison, J. Page, S. Church, D.
Small Animal Gastroenterology 3rd Edition: Editors Strombeck, D. R. Guilford, W. G.; page 318-352.
Textbook of Medical Physiology 10th Edition: Editors Guyton and Hall; page 718-771.
Textbook of Veterinary Internal Medicine 6th Edition: Editors Ettinger, S. J. Feldman, E. C.; 1290-1421.

1. What are the two main functions of the cells in the Crypts of Leiberkuhns:
   a. production of new epithelial cells and absorption of fluid and electrolytes
   b. production of new epithelial cells and secretion of fluid and electrolytes
   c. sloughing of old epithelial cells into the intestinal lumen and absorption of fluid and electrolytes
   d. sloughing of old epithelial cells into the intestinal lumen and secretion of fluid and electrolytes

2. Permeability of the intestinal mucosa is greatest in which section of the gastrointestinal tract:
   a. duodenum
   b. jejunum
   c. ileum
   d. colon

3. What are the two main neurotransmitters that stimulate secretion by enterocytes (crypt cells) in the small and large intestine:
   a. acetylcholine and noradrenaline
   b. acetylcholine and vasoactive intestinal peptide.
   c. somatostatin and opioids
   d. somatostatin and vasoactive intestinal peptide

4. The most common type of diarrhoea in cats and dogs on a pathophysiologic basis is:
   a. Abnormal motility
   b. Abnormal mucosal permeability.
   c. Osmotic.
   d. secretory

5. The most common motility abnormality associated with diarrhoea in dogs is:
   a. hypermotility due to increased segmental contractions
   b. hypermotility due to increased peristalsis
   c. hypomotility due to decreased segmental contractions
   d. hypomotility due to decreased peristalsis

Readers are invited to answer the questions as part of the RCVS CPD remote learning program. Answers appear on page 99.