MECHANISMS OF DIARRHOEA

- **diarrhoea = presence of excess water in faeces relative to faecal dry matter**
- **dysentery = diarrhoea with haemorrhage**

- diarrhoea usually results from an absolute increase in faecal water
- diarrhoea is often triggered by inflammation of the intestines

- the following terms indicate the level of intestine affected by inflammation:

  - **enteritis =** inflammation of the **small intestine**
  - **duodenitis =** inflammation of the **duodenum**
  - **jejunitis =** inflammation of the **jejunum**
  - **ileitis =** inflammation of the **ileum**
  - **typhlitis =** inflammation of the **caecum**
  - **colitis =** inflammation of the **colon**
  - **proctitis =** inflammation of the **rectum**

Causes of Diarrhoea

- there are numerous specific causes of diarrhoea in domestic animals:

  - parasites – e.g. whipworms, hookworms, coccidia, *Cryptosporidium* spp., *Giardia* spp.
  - viruses – e.g. canine and feline parvoviruses, bovine viral diarrhoea (BVD) virus, rotaviruses, coronaviruses
  - bacteria and/or bacterial toxins – e.g. salmonellae, *E. coli, Clostridium* species
  - other toxins – e.g. heavy metals
  - fungi
  - algae
  - ischaemia
  - sterile inflammation – e.g. food hypersensitivity, inflammatory bowel disease
  - neoplasia – e.g. intestinal lymphoma
  - hyperosmolar luminal contents – e.g. magnesium sulfate, undigested milk, excess carbohydrates in herbivores

Consequences of Diarrhoea

- loss of solutes and water in diarrhoea may result in:

  - **severe electrolyte depletion** – e.g. hyponatraemia, hypokalaemia
  - **acid-base imbalance** – especially metabolic acidosis from loss of bicarbonate ions in faeces
  - **dehydration**
  - potentially fatal **hypovolaemic shock**

Intestinal Water Absorption in Health

- in health, electrolytes and water are continuously secreted and absorbed across the small and large intestinal mucosa

- undifferentiated crypt epithelial cells of the small and large intestinal mucosa secrete large volumes of water and electrolytes (Cl^-, K^+, HCO_3^-) when stimulated by hormones and neurotransmitters (e.g. vasoactive intestinal peptide, serotonin, neurotensin and acetylcholine)

- most of the water absorption takes place in the **small intestine** (**all species**) and in the **proximal colon** (**carnivores**), the **spiral colon** (**ruminants** and **pigs**) and the **small colon** (**horses**)

- water absorption by mucosal enterocytes is passive and follows osmotically the active transport of electrolytes (especially Na^+) and nutrients (e.g. amino acids and glucose in the small intestine, volatile fatty acids (VFA) in the large intestine of herbivores)
- sodium absorption is an active, transcellular, ATP-dependent process, whereby Na^+ is absorbed against a concentration gradient and exchanged for K^+ or H^+ ions
- Cl^- is often absorbed with Na^+

- the **small intestinal mucosa** is **highly permeable ("leaky")** to the passive movement of small ions and water, despite the presence of tight junctions between adjacent surface enterocytes towards their apices
- in health, there is considerable passive movement of water osmotically towards the luminal content from the circulation in the proximal small intestine
- the permeability of these tight junctions is influenced by Starling forces (hydrostatic and oncotic pressures in capillaries and in the interstitium) so that absorbed fluid and solutes may subsequently leak back into the small intestinal lumen
- e.g. in congested small intestinal segments, increased hydrostatic pressure in capillary beds can promote oedema of the lamina propria and thence leakage of water and ions back into the bowel lumen
- in health, the small intestinal luminal content is usually isosmolal with plasma and interstitial fluid

- the **large intestinal mucosa** has ultimate responsibility for absorbing water and electrolytes to minimise their loss in faeces
- in health, large intestinal crypt cells have a secretory function and surface enterocytes are absorptive
- destruction of surface epithelium → rapid migration of immature crypt cells to the surface → increased secretion and decreased absorption
- only a relatively small absolute decrease in net absorption by the large intestine can lead to diarrhoea

- the **large intestinal mucosa is not leaky** and is therefore more efficient than the small intestinal mucosa in absorbing water and electrolytes → faecal water may be hypotonic relative to plasma
- faeces normally contain a higher K^+ and lower Na^+ concentration than does plasma

- **in health, water absorption in the small and large intestine exceeds secretion** (Figure 1)

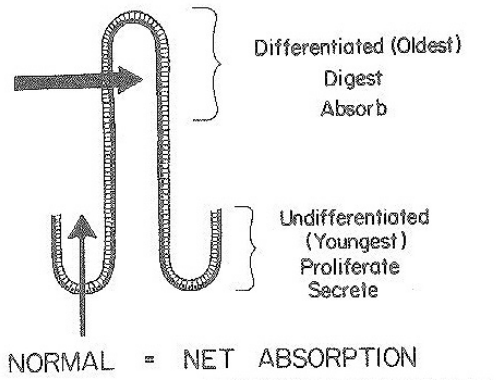

Figure 1 – Net absorption of water occurs in health across the small (and large) intestinal mucosa

Reference: HW Moon. Mechanisms in the pathogenesis of diarrhea: a review. *J Am Vet Med Assoc* 172:443-448 (1978)

Table 1 – Clinical Signs of Small Intestinal versus Large Intestinal Diarrhoea

Clinical Sign	Small Intestinal Diarrhoea	Large Intestinal Diarrhoea
Frequency of defaecation	Normal to mildly increased (2-3 x normal/day)	Usually increased (> 3 x normal/day)
Urgent defaecation	Uncommon	Common
Faecal volume	Often increased	May be decreased (due to increased frequency of defaecation)
Vomiting	May occur and is usually associated with eating	Uncommon (unrelated to eating if present)
Weight loss	Common	Rare except in malignancy and other severe infiltrative disorders
Appetite	Variable	Usually normal but may be decreased or rarely increased
Steatorrhoea	May be present	Absent
Mucoid faeces	Rare except with ileal pathology	Common
Tenesmus/dyschezia	Uncommon but possible in chronic cases	Common
Melaena	Possible	Absent
Haematochezia	Absent	Common

Small Intestinal Diarrhoea versus Large Intestinal Diarrhoea

- clinical signs often provide a clue as to whether the diarrhoea is chiefly referable to dysfunction of the small intestine or the large intestine (Table 1)

- illthrift, flatulence, borborygmus (increased gut sounds), abdominal pain, oedema and ascites are more commonly seen in animals with small bowel diarrhoea than with large bowel diarrhoea
- small bowel diarrhoea is usually free of grossly visible mucus or fresh (red) blood
- dark tarry faeces (**melaena**) suggest either swallowed blood (e.g. from the respiratory system) or upper gastrointestinal bleeding

SMALL INTESTINAL DIARRHOEA

- **three major mechanisms are responsible for small intestinal diarrhoea:**

    - **hypersecretion (secretory diarrhoea)**
    - **increased mucosal permeability (exudative diarrhoea**
    - **malabsorption (malabsorptive diarrhoea)**

- more than one of these mechanisms may contribute simultaneously to diarrhoea

- **osmotic drag of water** towards the luminal contents contributes to many forms of small intestinal diarrhoea, especially malabsorptive diarrhoea

- **small intestinal hypermotility** may also contribute to diarrhoea (by decreasing the intestinal transit time and hence the opportunity for digestion and absorption of nutrients) but is usually not a primary mechanism responsible for diarrhoea in domestic animals
- hypermotility may in fact be a response to increased fluid volume in the intestinal lumen

Hypersecretion (Secretory Diarrhoea)

- in hypersecretion, secretion of water and electrolytes by the intestinal mucosa exceeds its absorptive capacity whilst the integrity of the mucosa is maintained

- hypersecretion is most often due to the action of **bacterial enterotoxins** produced by:

    - enterotoxigenic *Escherichia coli* (ETEC colibacillosis) (Figure 2)
    - some *Salmonella* spp.
    - *Yersinia enterocolitica*
    - *Shigella* spp.
    - *Campylobacter jejuni*
    - *Vibrio cholerae* (humans)

- the heat-labile toxin (LT) of ETEC *E. coli* and the enterotoxins of *V. cholerae* and *C. jejuni* → increased intracellular [cAMP] → increased intracellular [Ca^{2+}] → decreased Na^{+} absorption by enterocytes (and hence decreased passive water absorption) and opening of Cl^{-} channels in crypt epithelial cells → secretion of Cl^{-} and water into the bowel lumen → diarrhoea

- the enterotoxin of *Y. enterocolitica* and the heat-stable toxin (ST) of ETEC *E. coli* → increased intracellular [cGMP] → comparable effects

- hypersecretion of the intestinal mucosa may also be caused by **local release of soluble factors** promoting secretion of Cl^- and water and impaired Na^+ and water absorption (e.g. prostaglandins, histamine, serotonin, vasoactive intestinal peptide, acetylcholine from enteric nerves)

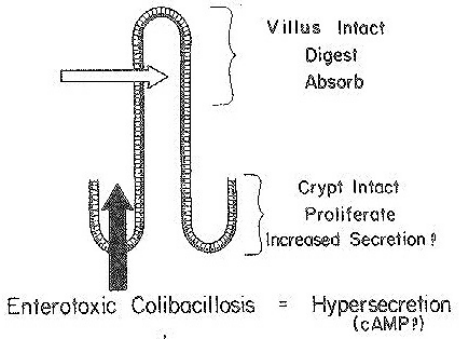

Figure 2 - Hypersecretory diarrhoea due to enterotoxigenic *E. coli*

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Enterotoxigenic E. coli

- enterotoxigenic *E. coli* (ETEC) are common cause of diarrhoea in neonatal lambs, calves and piglets
- the bacteria adhere to small intestinal enterocytes via **pilus antigens** (e.g. K88 in piglets, K99 in piglets, calves and lambs) so that the bactera are not dislodged by peristalsis
- **gross lesions** - dilated, flaccid small intestinal loops with excess yellow-white, watery to pasty contents
- **microscopic lesion** - adherence of small Gram-negative bacilli to small mucosal surface enterocytes; the mucosa is otherwise histologically normal

Increased Mucosal Permeability (Exudative Diarrhoea)

- **mucosal necrosis, erosion or ulceration** → direct leakage of plasma proteins, blood and inflammatory exudate into the bowel lumen (compounded by malabsorption due to loss of absorptive enterocytes)
  - e.g. salmonellosis
  - e.g. enteric clostridial infections
  - e.g. coccidiosis
  - e.g. swine dysentery in pigs due to infection with *Brachyspira hyodysenteriae*
  - e.g. infiltrative intestinal diseases such as intestinal lymphoma, Jöhne's disease, histiocytic ulcerative colitis in dogs

- **oedema of the small intestinal lamina propria** → leakage of fluid and large macromolecules into the intestinal lumen via leaky tight junctions between small intestinal enterocytes → diarrhoea

- e.g. hypoalbuminaemia → decreased plasma oncotic pressure in capillaries of the small intestinal villi
- e.g. increased hydrostatic pressure in small intestinal capillaries in right-sided congestive heart failure, portal hypertension, or hypervolaemia
- e.g. obstruction of small intestinal efferent lymphatics in intestinal lymphangiectasia
- e.g. increased vascular permeability associated with inflammation of the intestinal mucosa

- increased mucosal permeability due to any of the above mechanisms may lead to **protein-losing enteropathy**
- luminal loss of plasma proteins, particularly albumin → increased luminal osmolarity → osmotic drag of water → diarrhoea

Malabsorption (Malabsorptive Diarrhoea)

- e.g. **magnesium sulfate** (used therapeutically as a laxative) → poorly absorbed by the small intestinal mucosa → osmotic drag of water into the intestinal lumen → diarrhoea

- e.g. **primary maldigestion of nutrients** → failure of absorption of undigested substrates → osmotic drag of water → diarrhoea
- may lead to **steatorrhoea** (undigested lipid in faeces), **creatorrhoea** (undigested proteins in faeces) and/or **amylorrhoea** (undigested carbohydrates in faeces)
- may lead to malabsorption of fat-soluble vitamins (A, D, E and K)
- may lead to malabsorption of calcium, magnesium and zinc due to sequestration in soaps within the bowel lumen

- **causes of primary maldigestion** include:

  - **achlorhydria** or **hypochlorhydria**
    - e.g. neonates
    - e.g. animals with chronic gastritis/abomasitis → decreased hydrochloric acid production → impaired gastric phase of digestion → **small intestinal bacterial overgrowth (SIBO)** → competition for nutrients, decreased activity of intestinal brush border enzymes and often villous atrophy → diarrhoea

  - **gastric hyperacidity**
    - e.g. mast cell tumours or gastrin-secreting pancreatic islet cell tumours in dogs → increased acidity of the proximal small intestine → decreased activity or denaturation of pancreatic digestive enzymes, precipitation of bile salts, decreased activity of intestinal brush border enzymes and villous atrophy → diarrhoea

  - **exocrine pancreatic insufficiency** – especially dogs and, to a lesser extent, cats; often complicated by small intestinal bacterial overgrowth (SIBO)

  - **complete bile duct obstruction with insufficient bile salts** in the duodenum for emulsification, digestion and absorption of fats

  - **deficiencies of enterocyte microvillous enzymes** - e.g. maltase in neonates and ruminants; sucrase in ruminants; lactase in older animals

- e.g. attaching and effacing *E. coli* – attachment to enterocytes may damage the microvilli and glycocalyx → disturbed membrane digestion
- e.g. neomycin may cause fragmentation of enterocyte microvilli and destruction of the glycocalyx

- e.g. **short bowel syndrome** (following surgical resection of > 75-85% of the small intestine) → reduced absorptive area → unabsorbed substrates → osmotic drag of water → diarrhoea

- e.g. **small intestinal villous atrophy** → reduced absorptive area → unabsorbed substrates → osmotic drag of water → diarrhoea

- **villous atrophy is a common response to small intestinal mucosal injury**
- **mechanisms responsible for villous atrophy** are:

  - **increased loss of enterocytes from villi**
  - **necrosis or impaired mitosis of crypt stem cells**
  - **dysregulation of crypt stem cell proliferation and enterocyte maturation**

Increased Loss of Enterocytes from Villi

- e.g. rotaviral infections – target mature enterocytes towards the apices of villi (Figure 3)
- e.g. coronaviral infections – target all villous enterocytes
- e.g. intestinal coccidiosis – with protozoal replication within villous enterocytes
- e.g. enteropathogenic *E. coli*
- e.g. *Cryptosporidium* spp.
- e.g. transient ischaemia (> 5-10 minutes' duration but < 2-4 hours)

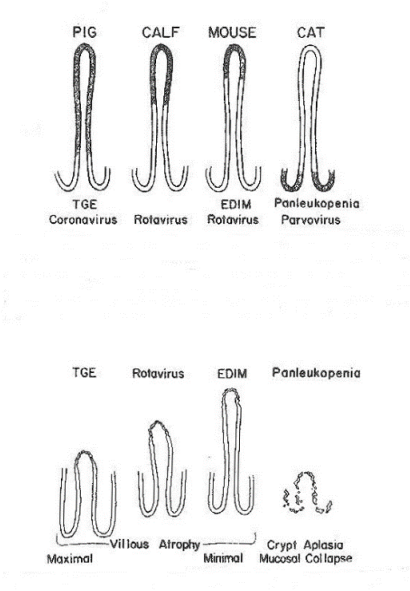

Figure 3 – Predilection sites for small intestinal mucosal injury by coronaviruses, rotaviruses and parvoviruses

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- within minutes of loss of surface enterocytes, adjacent surviving enterocytes flatten out and extend laterally to cover the defect; this is mediated by local growth factors and by *trefoil factor* produced by mucosal goblet cells
- villi contract and become stumpy and covered by attenuated squamous, cuboidal or low columnar cells
- +/- lateral or apical fusion of adjacent villi
- the proliferative compartment (crypt stem cells) is unaffected
- the lost enterocytes are replaced within a few days by mitotic division of crypt stem cells
- within 12-24 hours, see hypertrophy and hyperplasia of crypt cells → progressive repopulation of villous enterocytes → progressive elongation of villi with return to normal absorption

Necrosis or Impaired Mitosis of Crypt Stem Cells

- e.g. ionising radiation
- e.g. cytotoxic chemotherapeutic drugs
- e.g. T2 mycotoxins
- e.g. canine parvovirus 2 (Figure 3)
- e.g. feline parvovirus (feline panleukopenia virus) (Figure 3)
- e.g. bovine viral diarrhoea (BVD) virus
- e.g. rinderpest virus
- e.g. ischaemia of greater than 2-4 hours' duration (crypt necrosis is preceded by necrosis of villous enterocytes)

- surface enterocytes continue to slough at their normal rate but are not replaced by mitotic division in the crypts → eventual villous atrophy or collapse, with the mucosal surface lined by attenuated surviving enterocytes
- within a few days, see compensatory hypertrophy and hyperplasia of surviving crypt stem cells
- locally extensive crypt necrosis → mucosal erosion or ulceration → luminal leakage of protein and blood, malabsorption +/- secondary invasion by bacteria or fungi, +/- repair by granulation tissue → scarring (fibrosis) and narrowing (stenosis) of the intestinal lumen

Dysregulation of Crypt Stem Cell Proliferation and Enterocyte Maturation

- associated initially with hypertrophy/hyperplasia of crypt cells (possibly stimulated by cytokines or nitric oxide released by activated T lymphocytes in the lamina propria)
- later associated with atrophy of villi (due to premature exfoliation of enterocytes close to the crypt openings or low on the villi)
- enterocytes also do not differentiate fully → maldigestion and malabsorption of nutrients

- common in chronic persistent enteritis caused by nematodes, coccidia, *Giardia* spp., food hypersensitivity, inflammatory bowel disease, chronic granulomatous enteritis (e.g. Jöhne's disease) and intestinal lymphoma

- irrespective of the cause/mechanism, **villous atrophy → malabsorption of nutrients** → osmotic drag of water → diarrhoea
- loss of mature differentiated villous enterocytes may also → **maldigestion** due to loss of brush border enzyme activity

LARGE INTESTINAL DIARRHOEA

- the major mechanisms responsible for large intestinal diarrhoea are hypersecretion, increased mucosal permeability and osmotic drag of water

Hypersecretion

- **bile salts** are normally absorbed in the ileum by active transport
- ileal mucosal disease may result in inadequate bile salt absorption
- bile salts entering the colon → colonic hypersecretion of Cl^- and hence water (via a cAMP-dependent mechanism) → diarrhoea

- **enterotoxins** of such bacteria as *E. coli* and *Salmonella, Shigella* and *Campylobacter spp*. can cause colonic hypersecretion prior to the appearance of obvious mucosal damage

Increased Mucosal Permeability

- increased mucosal permeability may result from erosive and ulcerative typhlocolitis (e.g. salmonellosis, swine dysentery) and from infiltrative diseases of the large bowel (e.g. intestinal lymphoma, Jöhne's disease, histiocytic ulcerative colitis in dogs)

- in **steatorrhoea** due to lipid maldigestion or malabsorption in the small intestine, **excess fatty acids** entering the colon → mild damage to surface enterocytes and increased mucosal permeability

Osmotic Overload

- in suckling neonates, small intestinal maldigestion or malabsorption may allow entry of **lactose** into the colon where it is fermented by bacteria → VFA production → osmotic drag of water → additional faecal water loss
- lactose itself acts osmotically to draw fluid and electrolytes into the bowel lumen
- fermentation products of lactose may also cause colonic hypersecretion

- comparable osmotic overload of the colon may also occur in ruminants and horses with **excess intake of carbohydrates** (grain overload) or in animals with **intestinal maldigestion or malabsorption of carbohydrates**
- bacterial fermentation of the excess carbohydrate → excess VFA production → overwhelmed colonic buffering capacity via bicarbonate secretion → decreased luminal pH → altered microflora with predominance of bacteria producing lactic acid → osmotic drag of fluid by lactic acid into the lumen → diarrhoea