Food intolerance refers to any abnormal physiological response to a food or food additive, believed not to be immunological in nature. Mechanisms include food toxicity, pharmacological reactions, metabolic reactions, dysmotility, dysbiosis, physical effects and non-specific dietary sensitivity. Food intolerance reactions are variable, typically dose-dependent, and can occur at any age. Signs may arise at any time, sometimes several hours or days after consumption of the offending food item, and can last for hours or days. Dietary indiscretion and non-immunological food intolerance are probably more common in dogs than true dietary hypersensitivity. Hopefully, with a greater knowledge of the different pathophysiological mechanisms involved, we will become better at recognising, preventing and managing adverse food reactions.

INTRODUCTION

Food intolerance refers to any abnormal physiological response to a food or food additive, believed not to be immunological in nature, and has been reported to include food poisoning, food idiosyncrasy, direct food toxicity, pharmacological reaction or metabolic reaction (Anderson 1986, Halliwell 1992). These categories originate in human medicine, their application tends to be rather haphazard, and there is considerable overlap between them. Idiosyncratic reactions occur, by definition, sporadically and unpredictably, and do not refer to, nor describe, a particular pathophysiological mechanism. Most food intolerance reactions could, arguably, be described as idiosyncratic. Although a recent classification has attempted to define more clearly the underlying pathological mechanisms involved (Fig. 1; Table 1), in most clinical cases, the mechanism remains undetermined (Cave 2013).

The terminology used to describe adverse reactions to foods is confusing because of variations in interpretation of the terms (Reedy et al. 1997). An adverse food reaction, defined as a clinically abnormal response attributed to the ingestion of a food or food additive, is categorised in human medicine as either food allergy or food intolerance, terms for which strict definitions have been proposed (Anderson 1986). These definitions have largely been adopted by the veterinary world (Wills 1991, Gaschen & Merchant 2011), and much has been written in the veterinary scientific literature on food allergy (Cave 2013, Miller et al. 2013). In contrast, relatively little information can be found on food intolerance.

The prevalence of adverse food reactions in dogs and cats is largely unknown, but in one literature review was found to be between 1 and 2% of dogs presented to a primary care veterinarian, and under 1% of cats presented to a university hospital with any disease (Olivry & Mueller 2017). Food intolerance and dietary indiscretion (ingestion of inappropriate materials) are probably more common in dogs than true dietary hypersensitivity (Day 2005).

CLINICAL FEATURES OF FOOD INTOLERANCE

Food intolerance reactions in humans and animals are variable, typically dose-dependent, and can occur at any age. Signs may arise at any time, sometimes several hours or days after consumption of the offending food item, and can last for hours or days (Wills 1991, Turnbull 2014). The differential diagnosis of food intolerance is broad (Foil 1988, Zopf et al. 2009), there are no specific diagnostic tests, and identifying culprit foods can be challenging because several food groups may be implicated in the same individual. Objective testing for food intolerance requires double-blind, placebo-controlled food challenge but is rarely done (Turnbull 2014).

In people, intolerance reactions to food are reported to affect the skin, gastrointestinal tract, respiratory tract and central nervous system (Allen et al. 1984, Hodge et al. 2009, Turnbull 2014). Specific food intolerance has been implicated in many human conditions including irritable bowel syndrome (IBS) (Turnbull 2014) and eczema (Atherton et al., 1978, Hunter 1991).

Clear examples of food intolerance in animals are rare and often anecdotal (Hall 1994). IBS has not been unanimously defined in veterinary medicine, but a syndrome resembling human IBS has...
Some cats and dogs with colitis can be maintained in long-term remission, and the severity and chronicity of colitis modified, by using diet alone (Simpson 1998) suggesting the involvement of food in the pathogenesis. “Diet-responsive enteropathy” has been reported to encompass both food intolerance and food allergy (Simpson 2013a), but some dogs and cats may also benefit from a changed intake of dietary fibre, an improved ratio of n6 to n3 fatty acids, inclusion of probiotics and/or prebiotics, or simply from being fed a more digestible diet (Leib 2000, Gaschen & Allenspach 2013, Swallow 2017). Whether such dietary manipulations reduce the incidence of food intolerance reactions in these animals or merely reduce the severity of what might be mild inflammatory bowel disease is uncertain.

PATHOMECHANISMS OF FOOD INTOLERANCE

Food toxicity
Food toxicity (poisoning) is a term used generally to refer to reactions caused by microbial contamination (Cave 2013). However, plant-derived toxins, nutrient excess, metals, specific foods, toxins involved in the food manufacturing process, and toxins produced during storage resulting from microbial spoilage, can also result in food toxicity (Roudebush et al. 2000).

Microbial contamination
Many of the bacteria causing foodborne illnesses in people have the potential to cause disease in animals, although foodborne diseases in household pets are considered rare (Dillion 1986).

Food infection
Food infection may arise following ingestion of viable bacterial cells by a susceptible dog or cat. For clinical disease to occur, bacterial cells must replicate to pathogenic numbers. This typically takes 12 to 24 hours after ingestion of contaminated food. Examples of pathogenic bacteria include Salmonella species, Escherichia coli, and Campylobacter species. Healthy dogs and cats are reported to be fairly resistant to the pathogenic effects of these bacteria (Miller & Cullor 2000). However, they are among the species most sensitive to the effects of aflatoxin, a mycotoxin produced by Aspergillus species (Miller & Cullor 2000). Maize, peanuts, cottonseed and grains are potential sources of aflatoxins in pet foods. The principal
target organ is the liver, and clinical signs include severe gastrointestinal disturbances, jaundice and haemorrhage. Deoxyxynivalenol, DON (vomitoxin), a common mycotoxin contaminant of maize, wheat and other cereals, has been identified in commercial pet foods (Talcott 2013, Carrión & Thompson 2014), and can cause anorexia, vomiting and bloody diarrhoea in the dog, making it an important differential for canine parvovirus infection (Cave 2013).

Ingestion of mouldy foods, including grains, walnuts, almonds and peanuts, has been associated with seizures in dogs. The most common source of “tremorgenic mycotoxins” is the mould, Penicillium, found in decomposing food and vegetable matter (Gfeller & Messonier 1998, Barker et al. 2013).

### Plant-derived toxins

#### Oxalic acid

Oxalic acid and its salts occur as end-products of metabolism in a number of plant tissues, which, if eaten, may have an adverse effect because of the ability of oxalates to bind calcium and other minerals. Although oxalic acid is a normal end-product of mammalian metabolism, the consumption of additional oxalic acid may cause stone formation in the urinary tract. In humans, diets low in calcium and high in oxalates are not recommended (Noonan & Savage 1999).

Lower urinary tract stones are more common in dogs and cats than in humans (Syme 2012). The prevalence of calcium oxalate stones, the second most common type (after struvite calculi) found in companion animals, increased in dogs fairly steadily in the three decades leading up to 2012, and in cats quite dramatically between 1981 and 2002. One proposed reason for this is a change in diet. In the 1980s, in an attempt to reduce the prevalence of struvite calculi, most commercial brands of pet food (especially feline diets) were essentially reformulated to be more acidifying and to contain less magnesium. It is possible that there was also a shift in owner-preference to feeding more dry (i.e. “kibble”) rather than moist (i.e. canned or sachet) formulations (Syme 2012).

High levels of oxalates and anthraquinone glycosides in rhubarb, spinach and beetroot can cause gastroenteritis in dogs (Roudebush et al. 2000).

#### Phytic acid

Phytic acid is the major storage form of phosphorus in cereals, legumes, oil seeds and nuts (Gupta et al. 2015). Beneficial activities include effects on calcification and kidney stone formation, and lowering of blood glucose and lipids. However, it chelates micronutrients reducing bioavailability in monogastric animals such as humans, dogs and cats, which lack the enzyme phytase in their digestive tract (Schlemmer et al. 2009).

High levels of dietary phytate may hinder intestinal zinc absorption in dogs. Historically, most cases of zinc-responsive dermatosis in dogs were associated with feeding poor quality, cereal- or soy-based dry foods, the effects of which may have been exacerbated in some animals by a simultaneous inherent defect of zinc absorption (Watson 1998).

### Nutrient excess

Safe upper limits of vitamins and minerals for inclusion in commercial pet foods are often unknown (Morris et al. 2012, Davies et al. 2017). Furthermore, dogs and cats may react adversely to food supplements, both natural and synthetic, given by well-meaning pet owners (Miller & Cullor 2000). Supplements containing fat-soluble vitamins should be used with care because of the potential for hypervitaminosis syndromes, particularly hypervitaminosis A in cats (Polizopoulou et al. 2005) and hypercalcaemia following hypervitaminosis D in dogs (Nakamura et al. 2004, Mellonby et al. 2005).

### Metals

Lead, zinc, cadmium and arsenic are involved in most foodborne metal toxicities in dogs and cats (Miller & Cullor 2000). Resulting clinical syndromes depend on age, dose ingested and length of exposure. Metals can accumulate in plants and animals, and have been demonstrated in commercial pet foods (Edwards et al. 1979, Mumma et al. 1986). A definitive diagnosis of metal toxicity is based on finding toxic levels in the food, corresponding to the elevated levels in the patient’s tissues (Miller & Cullor 2000).

### Specific foods

Some human foods can cause adverse reactions in dogs and cats. Examples include onions, garlic, chocolate, nuts, grapes and raisins (Fig. 2) (Sutton et al. 2009, Cortinovis & Caloni 2016). These are discussed further under pharmacological reactions.

### Toxins from food manufacturing

#### Food additives

Additives are used in both human and pet food to help ensure quality, safety, texture, consistency, appearance, odour or taste (Pet Food Manufacturers Association 2018). They are often suspected by pet owners of causing health problems in their animals, but there are very few studies available to substantiate or refute these suspicions (Roudebush & Cowell 1992, Roudebush 1993).
Benzoic acid and propylene glycol are used as preservatives and humectants in food production. Benzoates have been identified as a cause of human atopic dermatitis (Van Bever et al. 1989), and have been linked to urticaria, asthma, rhinitis and anaphylaxis (Skypala et al. 2015). Propylene glycol has been documented to cause haematological abnormalities in cats (Hickman et al. 1990).

**Microbial spoilage**

Scombrootoxic poisoning is caused by ingestion of oily fish (e.g. mackerel, salmon, tuna, anchovies and sardines of the scombroid family) contaminated with bacteria that trigger the formation of high concentrations of histamine (Fig 3). Signs in people include skin problems (flushing and/or an erythematous urticarial rash affecting the face and upper trunk), headache, burning of the mouth and throat, vomiting and diarrhoea (Stratta & Badino 2013). In one account of normal dogs and cats being fed spoiled anchovies (Guilford et al. 1994, Chandler et al. 1995), adverse reactions to histamine in scombroid fish have been observed (Roudeshub 2010). Salivation, vomiting and diarrhoea have been reported in dogs and cats within 30 minutes of ingestion of raw anchovies (Guilford et al. 1994, Chandler et al. 2013). In one account of normal dogs and cats being fed spoiled skipjack tuna, no reactions were seen (Blonz & Olcott 1978).

**Pharmacological reactions**

Pharmacological reactions have been defined as adverse reactions to biologically active food chemicals, both natural and added (Allen et al. 1984). They do not refer to, nor do they describe, a particular pathophysiological mechanism, although many involve metabolic reactions.

**Histamine**

Histamine in food, at non-toxic doses, has been proposed as a major cause of food intolerance in humans, leading to many signs including pruritus, flushing, urticaria, gastrointestinal disorders, sneezing, rhinorrhoea, nasal congestion, asthma, headache, dysmenorrhoea, reduced muscle tone and cardiac arrhythmias (Wöhrl et al. 2004, Maintz & Novak 2007).

Certain foods, especially ageing or mature fish and meats, are known to be rich in histamine, whilst others have been found to encourage histamine release directly from tissue mast cells (Silla Santos 1996, Maintz & Novak 2007). In healthy people, dietary histamine can be rapidly detoxified by amine oxidases, principally diamine oxidase (DAO), and histamine N-methyltransferase (HNMT) (Maintz & Novak 2007). Small intestinal disorders can lead to reduced DAO formation (Forget et al. 1984) and some detergents (Sattler et al. 1987), and many commonly used drugs, inhibit DAO activity in both humans and dogs (Sattler et al. 1985).

The antibiotic, clavulanic acid, can profoundly inhibit porcine and human DAO (Sattler & Lorenz 1990). The clinical importance of this is unknown, but normally tolerated concentrations of dietary histamine may cause clinical signs of histamine intolerance (HIT) when the capacity for intestinal metabolism is reduced during oral treatment with clavulanate (Chandler 2013). Large differences in plasma DAO activity have been reported in cats (Fasceetti et al. 2002). There is no validated test for HIT, but determination of serum DAO activity may be a useful diagnostic tool (Music et al. 2011).

The importance and significance of HIT in small animal veterinary practice is unknown. Biogenic amines in canned pet food have been measured, although assessment of their biological effects was not possible (Pausen et al. 2000). In commercial pet foods, the highest levels of histamine have been found in moist, fish-based cat foods and those containing “fish solubles” – a by-product of fish canning and fish oil production (Guraya & Koehler 1991). The amount of histamine was deemed insufficient to cause histamine toxicity, but some of the foods contained enough histamine for the authors to conclude that idiosyncratic reactions in histamine-sensitive cats could not be excluded (Guilford et al. 1994). Vasooactive amines might also lower threshold levels for allergens in individual dogs and cats (Roudeshub 2010). Storage (for an unspecified duration) of opened cans of pet food, either under refrigeration or at room temperature, did not significantly increase the histamine content of most pet foods (Guilford et al. 1994).

**Salicylates**

Salicylate intolerance has been reported in people (Baenkler 2008) and may be a factor in 2 to 7% of all human patients with inflammatory bowel disease and food allergies (Raithel et al. 2005). Signs include respiratory problems, urticaria, eczema and gastrointestinal disturbances. Examples of salicylates include salicylic acid, found naturally in many plant foods, and the synthetic product, acetyl salicylic acid, known commonly as aspirin (Swain et al. 1985).

Similar effects have not been reported in dogs and cats but direct effects on renal function have been seen in dogs given sodium salicylate at doses sufficient to produce concentrations in plasma comparable with those common in human salicylate toxicity (Quintanilla & Kessler 1973).  

**Methylxanthines**

Theobromine and caffeine can be toxic in dogs, especially to the central nervous and cardiovascular systems (Gauberg & Blumenthal...
Food intolerance in dogs and cats

1983, Simeon et al. 2002). Theobromine occurs in cacao seeds and in products such as chocolate, manufactured from cacao seeds. Theobromine is eliminated very slowly in dogs, thereby prolonging the clinical syndrome and increasing the risk of toxicity from repeated ingestion of small doses. Caffeine is found in tea, coffee, many soft drinks and some human medications (Fig 4).

Chocolate is the most common cause of methylxanthine toxicity in dogs (Cortinovis & Caloni 2016). Theobromine is the predominant toxin, with caffeine present in much lower concentrations. Dogs are more commonly affected than cats because of their indiscriminate eating habits (Gwaltney-Brant 2001). Polydipsia, vomiting, diarrhoea, bloating and restlessness usually occur within 6 to 12 hours of ingestion, followed in some cases by hyperactivity, polyuria, ataxia, tremors and seizures. Death may occur due to cardiac arrhythmias or respiratory failure.

Cocoa shell mulch, spread on gardens, also contains high levels of theobromine. It smells of chocolate and may be attractive to dogs (Finlay & Guiton 2005).

Macadamia nuts

Macadamia nut toxicosis has been reported in dogs but not in cats. The mechanism of action is unknown and the dose required to induce toxicity has not been established (Gwaltney-Brant 2013a, Hansen 2000).

Hops

Hops, used in brewing beer, may trigger marked hyperthermia, anxiety, tachycardia, tachypnoea, panting, vomiting, abdominal pain, seizures and death in dogs and cats. Signs may arise within hours of ingestion. The mechanism of toxicity is unknown, but may involve resins, essential oils, tannins and nitrogenous compounds, or their metabolites, thought to uncouple oxidative phosphorylation resulting in malignant hyperthermia (Gwaltney-Brant 2013b).

Grapes, raisins and sultanas

These fruits have been reported to cause renal failure, and sometimes death, in dogs. Ingestion of any quantity should be considered a potential clinical problem though individual variations in response may also occur (Campbell 2007, Cortinovis & Caloni 2016). Vomiting within 24 hours of ingestion is typical. Diarrhoea, anorexia, lethargy and abdominal pain have also been reported. The mechanism of toxicity is unknown.

Onions, garlic, leeks and chives

Onions, garlic, leeks and chives are members of the Allium family. They contain organosulphoxides, which are converted, by chewing, to a complex mixture of sulphur compounds; N-propyl sulphide is believed to be the principal toxin. The toxic effects of these foods are not eliminated by cooking, drying or processing, and both dogs and cats are reported to be susceptible to allium toxicosis. Ingestion of 5 g/kg of onion by cats and 15 to 30 g/kg by dogs may induce clinically important haematological changes (Cope 2005). Common signs, which may appear one or more days after eating, initially include vomiting, diarrhoea, abdominal pain, loss of appetite and depression, followed by pale mucous membranes, weakness, rapid respiratory and heart rates, jaundice and dark urine.

Xylitol

Xylitol is a sugar alcohol used as an artificial sweetener, antibacterial agent and flavour enhancer in many human foods, medical and dental care products (Cortinovis & Caloni 2016). It is also an ingredient of drinking water additives developed to promote dog and cat dental health (Murphy & Coleman 2012). In dogs, xylitol is a potent stimulator of insulin release. A dramatic, potentially fatal, reduction in blood glucose levels and liver failure have both been reported in dogs. Clinical signs of xylitol toxicity in dogs may relate to hypoglycaemia (e.g. lethargy, ataxia, collapse and seizures), hepatopathy (e.g. lethargy, icterus, vomiting and haemorrhage) or both. Vomiting is usually the initial sign (Murphy & Coleman 2012).

Metabolic reactions

Metabolic food intolerances are adverse reactions to a food or food component resulting from a defect in the metabolism of these foods or some substance therein, or from an effect of the food or food component on the body’s normal metabolic processes (Taylor & Hefle 2001). Most food intolerance reactions would be expected to fall into this category, and many examples have been reported in humans.

Carbohydrate intolerance

Deficiencies of small intestinal brush border, disaccharidase enzymes, transporter defects, and malabsorption and maldigestion can lead to carbohydrate intolerance in people (Raithel et al. 2013, Sanderson 2013, Canani et al. 2016). Brush border enzyme deficiency may be congenital or acquired following intestinal injury or disease. Food components escaping digestion in the human small intestine enter the colon, and become available for fermentation by gut microbes (Carding et al. 2015). For example, colonic and distal small intestinal bacteria rapidly fer-
Dysbiosis (disrupted microbiota)
The Gastrointestinal microbiota – the collection of microbes residing in the gastrointestinal tract – plays a critical role in maintaining the structural and functional integrity of the gut and in immune system regulation (Furusawa et al. 2013, Purich et al. 2013), helping to protect against invading pathogens, and providing nutritional benefits to the host (Maslowski et al. 2009, Suchodolski 2013, 2017).

Dysbiosis is associated with acute and chronic gastrointestinal inflammation in dogs, cats and humans (Honner et al. 2014, Schmitz & Suchodolski 2016), and may have far-reaching consequences on host health, not only in the gastrointestinal tract but also in the skin and other extra-intestinal organ systems (Sekirov et al. 2010, Brown et al. 2012, Suchodolski & Simpson 2013, Craig 2016).

Ingested food has a profound effect on the number, species, metabolic activity and distribution of the intestinal microbiota (Zentek et al. 2003, Cave 2013), and dysbiosis may be both a cause and an effect of food intolerance. However, our understanding of dysbiosis is in its infancy, and we cannot currently draw firm conclusions about the influence of diet on the microbiota and disease development in animals or people.

Physical effects
Foods that cause physical irritation, damage or motility problems in the gastrointestinal tract may predispose to constipation and acute colitis (Cave et al. 2009). Examples include bone, hair and wool, particularly in dogs not used to consuming carcasses. Dietary indiscretion (scavenging) can result in the ingestion of toxins, indigestible physical abrasive substances, excessive fat and compounds that can cause gastric fermentation (Cave 2013). Large amounts of sand, ingested, e.g. on the beach, can result in small intestinal obstruction, and may cause ulceration of the intestinal mucosa, haemorrhage and altered motility (Papazoglou et al. 2004, Moles et al. 2010).

Some foods may cause low-grade inflammation and increased intestinal permeability in human IBS (Bischoff et al. 2014). Zonulin, an endogenous protein similar to an enterotoxin elaborated by the bacterium, *Vibrio cholerae*, modulates intercellular tight junctions in the gut mucosa, and, thereby, intestinal permeability (Fasano 2011). When the finely tuned zonulin pathway is disrupted in genetically susceptible people, both intestinal and extra-intestinal disorders can develop (Fasano 2011). Increased

FIG 5. Milk intolerance is common in adult dogs and cats

Dysmotility
Motility disorders of the stomach can cause vomiting in dogs and cats (Simpson 2013b), and diets that are high in fat, highly viscous (e.g. soluble fibre), or contain poorly digestible starch, may prolong gastric retention and promote vomiting in some dogs (Lin et al. 1992, Cave 2013).

Insoluble, non-fermentable fibre (e.g. cellulose) increases faecal bulk and the frequency of defaecation in healthy people, but may be poorly tolerated and exacerbate constipation if there is impaired colonic motility. Whether the same is true in dogs and cats is uncertain (Cave 2013).

Highly fermentable fibre (e.g. pectin and guar gum) may lead to methane production in the colon. Constipation, small intestinal dysmotility and discomfort are aggravated by methane in people with IBS (Pimentel et al. 2006), and the induction of non-propulsive segmental contractions by methane may also induce dysmotility in dogs and cats (Cave 2013).
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In conclusion, our understanding of food intolerance is limited by the lack of specific testing, and the variability of clinical signs. Hopefully, with a greater knowledge of the different pathophysiological mechanisms involved, we will become better at recognising, preventing and managing not only food intolerance but also adverse food reactions more generally.

Conflict of interest

The author of this article has no financial or personal relationship that could inappropriately influence or bias the content of the paper.

Non-specific dietary sensitivity

Non-specific dietary sensitivity has been described in animals with poorly formed faces when fed certain types of commercial diet (Rolle et al. 2002, Zentek et al. 2002). The mechanism of the reaction is unclear although affected animals readily respond to appropriate dietary manipulation (Cave 2013).

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