Summary

Pancreatitis, or inflammation of the pancreas, is commonly seen in dogs and cats and presents a spectrum of disease severities from acute to chronic and mild to severe. It is usually sterile, but the causes and pathophysiology remain poorly understood. The acute end of the disease spectrum is associated with a high mortality but the potential for complete recovery of organ structure and function if the animal survives. At the other end of the spectrum, chronic pancreatitis in either species can cause refractory pain and reduce quality of life. It may also result in progressive exocrine and endocrine functional impairment. There is confusion in the veterinary literature about definitions of acute and chronic pancreatitis and there are very few studies on the pathophysiology of naturally occurring pancreatitis in dogs and cats. This article reviews histological and clinical definitions and current understanding of the pathophysiology and causes in small animals by comparison with the much more extensive literature in humans, and suggests many areas that need further study in dogs and cats.

Structure of the normal canine and feline pancreas

The pancreas is situated in the abdomen caudal to the stomach and is composed of: a left limb or lobe, which lies behind the greater curvature of the stomach and adjacent to the cranial aspect of the transverse colon; a right limb or lobe which lies just medial to the proximal duodenum and a body between these two limbs (Evans 1993; Saunders 1991) (figure 1). The structure of the pancreas of dogs and cats differs somewhat from humans: the left limb is much smaller in humans than in dogs and cats and is called the

'head' whereas the right limb is much larger in humans and is called the 'tail'. The distal part of the left limb of the pancreas in humans, which dips down behind the duodenum and varies in size and extent, is called the uncinate process (Lack 2003). Some veterinary reports use the human terminology to describe the canine pancreas, referring to the left limb as the 'head' and the right limb as the 'tail', although there is no recognised canine or feline equivalent of the uncinate process. The terms right and left limb and body are preferred in dogs and cats, to stress the anatomical differences from humans.

The exocrine acini comprise about 98% of the pancreatic mass in dogs and humans (Evans 1993; Motta et al. 1997). The endocrine islets comprise about 2% of pancreatic mass (Evans 1993). The acini are linked via a series of smaller ducts to two larger pancreatic ducts in most dogs: the larger duct is actually the accessory duct in dogs, which enters the duodenum at the minor duodenal papilla. The smaller duct is the pancreatic duct which enters the duodenum approximately 28mm cranial to the accessory duct and in close proximity to the bile duct at the major duodenal papilla (Evans 1993). The pancreatic ducts in most dogs do not join the bile duct before exiting in to the duodenum (Evans 1993). This anatomical arrangement differs from cats and humans where the pancreatic duct usually joins the common bile duct just before entering the duodenum at the Ampulla of Vater (Evans 1993; Lack 2003). A secondary minor, or accessory, pancreatic duct enters the duodenum separately in humans and about 20% of cats, although many cats do not have a second duct. Other anatomical variations exist in dogs but are uncommon: for example, some dogs have only one pancreatic duct and in

others the bile duct joins the pancreatic duct before exiting in to the duodenum as in cats (Evans 1993).

Definitions of acute and chronic pancreatitis:

a) Histological definitions

The differences between acute and chronic pancreatitis (CP) are histological and functional and not necessarily clinical. The clinical appearance of acute and chronic disease overlaps: thus it is possible to suffer recurrent acute pancreatitis which mimics chronic disease and it is not uncommon for CP to present initially as a clinically severe, apparently acute bout of pancreatitis after a long sub clinical phase of low grade disease has already destroyed much of the pancreatic parenchyma. This has long been recognized in humans (Etemad & Whitcomb 2001b) and more recently in dogs (Watson et al. 2010). Even more confusingly, it is suggested that many cases of CP start as recurrent, acute disease both in humans (Etemad & Whitcomb 2001b; Witt et al. 2007; Talukdar & Vege 2009) and in dogs (Bostrom et al. 2013).

The ‘gold standard’ for definitive diagnosis of pancreatitis and its definition as acute or chronic disease is histological (Etemad & Whitcomb 2001b; Watson et al. 2007) (fig 2). The histological definitions of acute and chronic pancreatitis used in humans are favoured by this author for small animal patients. Acute pancreatitis is associated with varying amounts of neutrophilic inflammation, oedema and necrosis (Lack 2003). At the severe end of the spectrum, it has a high mortality but if the patient recovers, it is potentially completely reversible both histologically and functionally. The key histological

features differentiating chronic from acute and recurrent acute pancreatitis are permanent, irreversible and typically progressive histopathological changes, particularly fibrosis and acinar loss as reported in humans (Etemad & Whitcomb 2001a; Lack 2003). These changes are also recognized and reported in dogs (Watson et al. 2007; Bostrom et al. 2013; Newman et al. 2006) and cats with CP (De Cock et al. 2007). The inflammatory cell infiltrate in CP can be mononuclear or mixed mononuclear and granulocytic. In humans, CP is very commonly associated with pancreatic ductular concretions and calcifications (stones) (Lack 2003; Etemad & Whitcomb 2001b). These pancreatic ductular stones are very rarely recognized in dogs and cats, although the reason for this is not known. Dogs have been shown to secrete what is known as 'pancreatic stone protein' into their pancreatic ducts but, unlike in humans, this does not precipitate in to stones (Bernard et al. 1991).

Differentiation of truly acute disease from an acute flare-up of chronic disease may not be important for initial management, but it is important to allow recognition of the potential long-term sequelae of chronic disease such as the development of exocrine pancreatic insufficiency (EPI) and diabetes mellitus (DM). Clear histological definition is also critical for future studies on the aetiology of pancreatitis in dogs and cats. The differentiation of acute and CP should be simple because the histological changes are distinct. However, pancreatic histology is often not indicated or performed in clinical cases because of the associated morbidity. In the past, many authors have assumed that dogs presenting acutely clinically all have 'acute' pancreatitis (Hess et al.

1998) and have considered that the presence on histology of pancreatic cell necrosis and/or a neutrophilic infiltrate is the hallmark of 'acute' disease, regardless of the potential concurrent presence of fibrosis and permanent pancreatic architectural changes. In a case-control study of fatal acute pancreatitis in dogs with histological confirmation involving 70 cases and 104 controls (Hess et al. 1998), 40% of the cases actually had acute pancreatic necrosis superimposed on fibrosis i.e. acute-on-chronic disease. In addition, statistical analysis showed that dogs in that study with fatal acute pancreatitis had significantly more historical evidence of prior gastrointestinal disease before their fatal bout than the control population of dogs, again supporting the suggestion of previous ongoing CP in many of the dogs (Hess et al. 1999). The question remains as to whether these previous gastrointestinal signs were due to CP, chronic enteritis or another disease. It is unknown whether there is a relationship between CP and small intestinal disease in dogs. An association between CP and enteritis has been described in cats (Weiss et al. 1996), although the reason remains unclear.

Chronic pancreatitis has long been considered to be more common than acute disease in cats (De Cock et al. 2007; Xenoulis & Steiner 2008) although recent studies have increased recognition of acute disease in this species (Armstrong & Williams 2012). Conversely, historically, acute pancreatitis was considered to be much more common than CP in dogs. However, more recently, studies where pancreatic histology has been undertaken in dogs have shown that CP is common in this species. One prospective pathology study found lymphocytic inflammation in 72.3% of 47 canine pancreata with

pancreatitis (Newman et al. 2004) and another prospective pathology study demonstrated 34% of old dogs euthanased in first opinion practice had evidence of CP on histology (Watson et al. 2007). A recent study designed to assess the sensitivity and specificity of serum markers of pancreatitis investigated 63 dogs with histologically confirmed disease. Only 5 of these dogs had purely acute pancreatitis with the other 58 having some histological evidence of chronic underlying disease (Trivedi et al. 2011). The evidence in the veterinary literature therefore suggests that CP is common in dogs but often presents acutely clinically.

Veterinary histological scoring schemes

Recently, veterinary researchers have attempted to follow the human lead and provide clear histological descriptions of pancreatitis in dogs and cats. However, there are no agreed histological standards for diagnosis of acute and CP in dogs and cats.

Two recent pathology studies of pancreatic lesions in dogs favour the human definition of chronicity and classed all dogs with fibrosis as CP, even if they had superimposed acute inflammation (Newman et al. 2004; Watson et al. 2007). A follow-up study by Newman et al (2006) suggested a histological grading system for canine pancreatitis in which a number of histological features were graded on each histological section between 0 and 3 where grade 0 = none of the section affected; grade 1 was up to 10% of the section affected; grade 2 was 10-40% of the section affected and grade 3 was over 40% of the section affected. The histological features graded were:

neutrophilic inflammation; lymphocytic inflammation; pancreatic necrosis; fat necrosis; oedema; fibrosis; atrophy and nodules. This grading system has subsequently been used by others in canine studies (Bostrom et al. 2013; Mansfield et al. 2012; Watson et al. 2011) but has yet to be extensively validated by independent pathologists.

In 2007, the histopathological characteristics of feline pancreatitis were reviewed and a scoring system was designed to grade the severity of pancreatitis (De Cock et al. 2007). Feline acute pancreatitis was characterized by neutrophilic inflammation and varying amounts of pancreatic acinar cell and peripancreatic fat necrosis. Feline chronic nonsuppurative pancreatitis was characterized by lymphocytic inflammation, fibrosis and acinar atrophy. An earlier feline pathology study divided feline acute pancreatitis in to two forms: acute necrotizing where there was significant fat necrosis and acute suppurative where fat necrosis was not a feature (Hill & Winkle 1993). In common with the confusion cited in the canine literature, those earlier studies also included some cases with concurrent interstitial fibrosis and lymphocytes and plasma cells (ie chronic changes) in the acute necrotizing group.

It is therefore clear that, although recent attempts have been made to improve the histological classification of canine and feline pancreatitis, much work remains to be done. It will be important in the future to produce clear, consensus histological standards for pancreatic disease, just as histological standards have been agreed for liver disease in dogs and cats (Rothuizen et al. 2006).

b) Clinical and functional definitions and non-invasive diagnosis of acute and chronic pancreatitis

The challenge in the diagnosis of acute and chronic pancreatitis in any species is that histology is often not performed because it is invasive and not judged as clinically justified. Therefore, in many cases in humans and small animals, presumptive diagnosis is made on the basis of functional changes together with clinical, clinicopathological and diagnostic imaging findings. Non-invasive scoring schemes have been developed in humans for diagnosis of both acute and chronic pancreatitis and have been validated and developed over many years to take account of advances in understanding of disease pathogenesis and diagnostic imaging techniques. No such schemes have been developed in veterinary medicine. However, they would be very valuable. Advanced imaging techniques such as computed tomography and magnetic resonance cholangiopancreatography are often used as part of the scoring schemes in humans. There is limited access to such advanced imaging techniques in veterinary medicine. However, even clinicopathological results and transcutaneous ultrasound are used in some human scoring systems (Banks et al. 2012) so development and validation of non-invasive scoring schemes should be a future goal in dogs and cats.

The Atlanta classification of human acute pancreatitis

Acute pancreatitis in humans has been classified clinically and non-invasively since 1992 using the Atlanta scheme (Bradley 1993). This has been updated by consensus to result in the 2012 revision of the Atlanta classification (Banks

et al. 2012). Using this scheme, the diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of the reference interval; and (3) characteristic findings of acute pancreatitis on contrast-enhanced CT and less commonly magnetic resonance imaging (MRI) or trans-abdominal ultrasonography. The revised Atlanta classification also attempts to define the severity of acute pancreatitis particularly with respect to associated organ failure and pancreatic necrosis. It recognizes two phases of acute pancreatitis: early and late disease. Severity of acute disease is defined as mild (no organ failure or local or systemic complications): moderate (with transient organ failure, local complications or exacerbation of co-morbid disease) or severe acute pancreatitis (with persistent organ failure and local complications including pancreatic necrosis). This classification clearly delineates the major factor associated with mortality in humans with acute pancreatitis; persistent (>48 hours) multi-organ failure. Multi-organ failure is also defined in the Atlanta classification with a scoring system relating to three organs: respiratory; cardiovascular and renal (Banks et al. 2012).

There is no published non-invasive diagnostic system for pancreatitis in dogs and cats. There have, however, been some limited attempts at severity scoring the canine disease once it has been diagnosed to attempt to predict prognosis and complications (Ruaux & Atwell 1998; Mansfield et al. 2008). These are small studies and limited to dogs so again there is much potential

for improvement and validation of these schemes for small animals in the future.

Non-invasive diagnostic criteria for human chronic pancreatitis

Non-invasive diagnostic criteria for CP in humans rely on a combination of functional and diagnostic imaging changes. The fibrosis and scarring in chronic disease are known to be progressive in humans, probably as a result of interference with pancreatic blood supply and blockage of small ducts (Etemad & Whitcomb 2001b). Recent pathology and clinical studies in dogs suggest fibrosis is also progressive in this species (Watson et al. 2010; Watson et al. 2007). This progressive loss of pancreatic tissue means that there is progressive loss of exocrine and/or endocrine tissue until the patient develops EPI and/or DM respectively. However, the pancreas has a tremendous functional reserve – even more than the liver – such that DM or EPI in humans usually only develop clinically after 80-90% of exocrine or endocrine tissue have been lost (Larsen 1993; DiMagno et al. 1973). The obvious problem therefore with relying on functional changes only to diagnose CP is that they will only be sensitive in end stage disease. Diagnosis of earlier disease relies on either more sensitive tests of early pancreatic functional loss (which currently do not exist) (Keller et al. 2009) or diagnostic imaging.

The human Cambridge classification of CP of 1984 considered classical findings on diagnostic imaging (endoscopic retrograde pancreatography, ultrasound and CT) (Sarner & Cotton 1984) together with some morphological and functional changes. The Cambridge classification has remained the gold

standard in Europe for the diagnosis of CP and more recent classifications have attempted to add to this with more details of history and function tests, together with the incorporation of the newer diagnostic imaging methods of endoscopic ultrasound and magnetic resonance cholangiopancreatography or more clinically relevant sub-groups (Etemad & Whitcomb 2001b; Büchler et al. 2009; Bagul & Siriwardena 2006) The Japanese Pancreas Society developed their own, slightly different, criteria in parallel in 1995 with updates in 2001 and 2010 (Shimosegawa et al. 2010). The difficulty with all these non-invasive scoring schemes for human CP is the fact that they are much more likely to give a diagnosis in more severe and more end-stage disease whereas diagnosis of early CP with less marked functional and structural changes remains a challenge.

Differentiating EPI in dogs due to pancreatic acinar atrophy from EPI due to end stage chronic pancreatitis

An important addendum to the discussion of functional changes with CP is to stress the importance in dogs of differentiating pancreatic acinar atrophy (PAA) from end stage CP as causes of EPI. There has been occasional confusion in the literature suggesting they are the same disease (Sutton 2005). However, they are clinically and histologically very distinctive. PAA is particularly recognized in young German shepherd dogs (GSDs), but also rough collies, English setters and sporadically in other breeds (Westermarck & Wiberg 2003; Westermarck & Pamilo 1989; German 2012). In GSDs with PAA, an autosomal mode of inheritance has been suggested (Westermarck 1980) although a recent study refutes this and suggests the inheritance is

more complex (Westermarck et al. 2010)

Histological studies in GSDs suggest that PAA is an autoimmune disease directed specifically against the acini (Wiberg et al. 2000). Therefore the islets are spared, and dogs with PAA are not typically diabetic. However, affected dogs do not respond to immunosuppressive therapy (Wiberg & Westermarck 2002). Most dogs develop the disease in young adulthood, but a proportion of GSDs remain subclinical for a prolonged period of time and present only late in life (Wiberg & Westermarck 2002). Importantly, the predominant histological change is pancreatic acinar atrophy with replacement of acinar tissue with fat, while islets remain – PAA is NOT characterised by pancreatic fibrosis and inflammatory cells are only seen in the early stages of the disease.

In contrast, end stage CP is characterised by fibrosis replacing pancreatic tissue, both acini and islets, and many dogs with end-stage CP also develop DM either before or after EPI as a result of concurrent islet cell destruction (Watson et al. 2010; Watson 2003). Dogs with CP also show lymphoplasmacytic inflammation throughout the disease process rather than only early in the disease (Watson et al. 2007; Bostrom et al. 2013). Dogs with EPI as a result of end-stage CP tend to be middle-aged to older medium- or small-breed dogs, particularly Cavalier King Charles spaniels (CKCS), English cocker spaniels, and Border collies (Watson et al. 2011; Watson et al. 2010). One study reported an increased prevalence of EPI in older CKCS (Batchelor et al. 2007) and, although the aetiology was unknown, end stage CP was suggested because of the older age at presentation of these dogs.

Pathophysiology of acute and chronic pancreatitis in dogs and cats

There has been an enormous amount of work on the pathophysiology of pancreatitis in the naturally occurring human disease and in experimental models in rodents and dogs. However, there are no studies in naturally occurring acute or CP in dogs and cats so the following discussion is based on the findings from human and experimental animal work. It will be important in the future to study the disease specifically in dogs and cats to increase our understanding of the pathophysiology in small animals.

Interaction between genes and environment

Key to understanding the pathophysiology of acute and CP is a realization that both diseases occur as a 'final common pathway' of a number of underlying mechanisms. The vast majority of cases of pancreatitis in humans occur as a result of a complex interaction of genes and environment (LaRusch & Whitcomb 2011) and it is very unusual for a single factor alone to cause pancreatitis. For example, heavy drinking is an important cause of acute and CP in humans, and yet only a small proportion of genetically susceptible alcoholics develop pancreatitis (LaRusch & Whitcomb 2011). Even hereditary pancreatitis in humans due to 'simple' point gene mutations has variable penetrance depending on the presence of concurrent genetic and environmental risk factors (Szabo & Sahin-Toth 2012).

Relationship between acute and chronic disease

The other important consideration is the relationship between acute (reversible) and chronic (progressive and irreversible) disease. Many cases of

CP result from recurrent acute disease. For example, cationic trypsinogen mutations in humans cause recurrent acute pancreatitis progressing to chronic disease (LaRusch & Whitcomb 2011). The failure of this acute disease to resolve and its propensity to lead to fibrosis and irreversible changes may depend on both the genetic make-up of the individual and the environment and particularly in humans, factors such as intake of alcohol and smoking (LaRusch & Whitcomb 2011). It is unclear how many cases of CP start as acute disease and how many are 'chronic' from the outset. The latter may sound odd, but any disease which starts as a lymphoplasmacytic infiltrate could be said to be chronic from the start, so autoimmune CP (IgG4 related disease – see below) could be defined as 'chronic' for this reason. However, even in autoimmune CP, the trigger for the disease to develop is unknown and could, in some cases, be an episode of acute pancreatitis.

Figure 3 gives a diagrammatic representation of the current understanding of the inter-relationship of acute and CP, genes and the environment.

Over-view of pathophysiology of acute pancreatitis

A detailed discussion of the molecular pathophysiology of pancreatitis is beyond the scope of this review. However, in summary, inappropriate early activation of proteases within the pancreas, particularly the zymogen trypsinogen to trypsin, is believed to be the final common pathway triggering pancreatic inflammation in most cases (LaRusch & Whitcomb 2011; Schneider & Whitcomb 2002). Inappropriate early activation of trypsin within the acinar cells activates other zymogens and causes autodigestion and severe inflammation. Pancreatic inflammation and peripancreatic fat necrosis

lead to focal or more generalized sterile peritonitis. The neighbouring gut wall becomes affected and there is a high risk of bacterial translocation from the gut lumen in both humans and dogs (Qin et al. 2009). Many recent studies implicate mitochondrial damage and oxidant release in the perpetuation of acute pancreatitis (Gerasimenko & Gerasimenko 2012; Maléth et al. 2012).

Recent studies in humans stress the importance of a compensatory anti-inflammatory response (known as CARS) in localising the inflammation to the pancreas and preventing systemic dissemination (Talukdar & Swaroop Vege 2011; Kylänpää et al. 2012). Mild acute pancreatitis is associated with CARS which is characterised by up regulation of anti-inflammatory cytokines such as IL10 and 11 (Kylänpää et al. 2012). It is suggested in humans that an excessive CARS may suppress the immune system enough to predispose to bacterial or fungal infection of pancreatitis necrosis, which is a relatively common and serious sequela to pancreatitis in humans. (Kylänpää et al. 2012; Talukdar & Swaroop Vege 2011). In contrast, infected necrosis is very rare in dogs and cats although it is occasionally reported (Marchevsky et al. 2000).

The pro-inflammatory response in pancreatitis in humans and rodents is characterised by generalised activation of proinflammatory cytokines such as the inducible transcription factor NF-κβ; TNF α and IL 6 and 8.(Kylänpää et al. 2012). A study in dogs also showed elevation in TNF □□in plasma in 31% dogs with severe acute pancreatitis (Ruaux et al. 1999). These cytokines lead to generalised neutrophil and monocyte activation resulting in damage to

vascular endothelium throughout the body, with ensuing tissue oedema and hypoxia. Organs with extensive capillary beds such as the lungs, kidneys and liver are particularly susceptible to damage (Talukdar & Swaroop Vege 2011). The coagulation cascade may also be activated ultimately resulting in DIC in some cases. IL 6 is a potent inducer of acute phase protein production in the liver such as c-reactive protein (Kylänpää et al. 2012). Pancreatitis is recognised as one of many diseases which results in increased c-reactive protein concentrations in dogs (Nakamura et al. 2000). It is clearly recognised in humans that mortality in severe acute pancreatitis is much more closely related to this multi-organ failure than to the apparent severity of the pancreatitis itself (Kylänpää et al. 2012; Talukdar & Vege 2009; Banks et al. 2012). Two studies also support this theory in naturally occurring pancreatitis in dogs: in one study of 60 dogs with acute pancreatitis, TNF α was elevated in 31% of dogs with severe disease and strongly associated with a lethal disease outcome (Ruaux et al. 1999). In the same dogs, the concentration of plasma α macroglobulin was found to be significantly reduced from normal, consistent with its consumption clearing circulating proteases, but there was no significant difference in α macroglobulin between severity groups (Ruaux & Atwell 1999). Taken together, these findings suggest also that the severity of the systemic inflammatory response is better correlated with outcome in dogs than the release of proteases from the pancreas.

Protection against trypsin activation

Premature activation of trypsin within the pancreas has the potential to cause severe pancreatic damage. Because of this, there are many layers of

protection in place to stop this happening. Many subtleties have been added to our knowledge of trypsin storage and activation as a result of studies of the pathophysiology of pancreatitis in humans and rodents. Disruption of these protective mechanisms underlie many genetic and environmental causes of pancreatitis. Trypsin is stored as an inactive zymogen, trypsinogen, in the pancreas and is activated in the small intestine by cleavage of a peptide (the trypsin activation peptide, TAP) from the trypsinogen molecule by the brush border enzyme enterokinase (Hall et al. 2005). In fact, in the small intestine, not only enterokinase, but also other activated trypsin molecules will activate trypsinogen by cleaving TAP. Recently, another pancreatic enzyme, chymotrypsin C, has also been implicated in activating trypsinogen in the small intestine. Interestingly, chymotrypsin C can either activate trypsin or inactivate it depending on the calcium concentration of the environment (Szabo & Sahin-Toth 2012).

An early breakthrough in the understanding of the pathogenesis of pancreatitis in humans was the discovery of mutations in the cationic trypsinogen gene which cause autosomal dominant hereditary pancreatitis (Etemad & Whitcomb 2001b; LaRusch & Whitcomb 2011). About 20 gain-of-function mutations in this gene have been identified in humans and they all cluster around calcium-binding sites which regulate trypsin activation. Calcium concentration is very low in acinar cells but high within the pancreatic duct and small intestinal lumen, favouring trypsin activation (LaRusch & Whitcomb 2011). Activation of trypsin is also pH dependent: although trypsin requires a relatively high pH to function (i.e the alkaline pH of the small intestine), its

activation appears to be exquisitely pH sensitive. The pH of pancreatic fluid within the pancreatic duct in humans and guinea pigs can vary between 6.8 and 8.0 and it has been shown that autoactivation of trypsinogen is relatively slow at pH 8.5 whereas autoactivation becomes progressively more rapid when the pH is decreased from 8.5 to 7 (Pallagi et al. 2011). These interesting results suggest that pancreatic bicarbonate secretion is not only important for neutralizing gastric acid in the duodenum but also for keeping pancreatic enzymes in an inactive state in the pancreatic ducts where the pH is higher than in the small intestine. The localization of key trypsin receptors in the pancreatic ducts are different in dogs compared to humans and guinea pigs (Pallagi et al. 2011). Therefore, studies of duct function in pancreatitis should not be directly extrapolated from these species to dogs and cats: species specific small animal studies are not yet available but are needed.

Trypsinogen is co-located within the pancreatic acinar cells with serine protease inhibitor Kazal type 1 (SPINK 1) previously known in the veterinary reports as pancreatic secretory trypsin inhibitor (Mansfield 2012). This protease inhibitor inhibits trypsin activation. Early descriptions of the pathophysiology of pancreatitis suggested this was an important mechanism for preventing trypsin autoactivation in the ‘normal’ pancreas. However, recent studies have suggested that SPINK1 is only expressed in large amounts in the context of ongoing inflammation when it does become an important protective mechanism (LaRusch & Whitcomb 2011). This may explain why mutations in SPINK1 alone in humans do not appear to be enough to cause

recurrent acute pancreatitis, but do increase the severity of recurrent pancreatitis caused by other mechanisms (LaRusch & Whitcomb 2011).

Other mutations in humans which predispose to pancreatitis but only when combined with other risk factors include a number of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) which are not severe enough to cause cystic fibrosis and mutations in the chymotrypsin C gene (LaRusch & Whitcomb 2011). There is also increasing focus in human medicine on the phenomenon of 'epistasis' whereby the effects of one gene modify the effects of another. For example, the concurrence of variants of SPNIK1 and CFTR can be synergistic (LaRusch & Whitcomb 2011). Severe mutations of CFTR result in cystic fibrosis which is an important cause of CP in humans because of duct blockage by the abnormal ductular secretion and changes in pH and calcium concentrations in this fluid (Wilschanski & Novak 2013).

Potential causes of acute and chronic pancreatitis in dogs.

Considering all the mechanisms contributing to trypsin activation discussed in the previous section, it is already possible to imagine a number of routes by which pancreatitis could be initiated and propagated. In humans, the causes of pancreatitis are often known, and there is increased understanding of the interaction of genetic susceptibility and environmental risk factors (LaRusch & Whitcomb 2011). The causes of acute and chronic pancreatitis in dogs and cats are usually unknown, largely to due lack of research, although a number

of risk factors have been identified in the literature and further research in small animals should elucidate aetiologies in the future.

Proposed risk factors for acute pancreatitis in dogs include breed (as detailed below); being overweight (Hess et al. 1999; Lem et al. 2008); being male or neutered female (Hess et al. 1999); being neutered or having previous surgery (Lem et al. 2008); hyperlipidaemia (Whitney et al. 1987; Xenoulis & Steiner 2010) and certain drugs (see below). In addition, concurrent endocrine diseases (DM, hyperadrenocorticism and hypothyroidism) were associated with an increased risk of fatal acute disease in one study (Hess et al. 1999). Epilepsy was also identified as a risk factor for acute pancreatitis in the same study, but it is unclear whether this was an association with the therapy rather than the disease.

Study of genetic predispositions to pancreatitis in dogs is at a very early stage and there are no studies to date in cats. It is very likely that genetic predispositions exist in dogs because clinical studies show significant breed prevalences: terriers have been reported to have an increased risk of acute disease (Hess et al. 1999). CKCS, boxers, cocker spaniels and Border collies appear to have an increased risk of chronic disease in the UK (Watson et al. 2007; Watson et al. 2010; Watson et al. 2011). In the USA, dogs classed by the American Kennel Club as toy/non-sporting dogs appear to have an increased risk of chronic disease (Bostrom et al. 2013). Studies of canine mutations predisposing to acute pancreatitis have focussed on miniature schnauzers. Studies in the USA have shown no mutations in the cationic

trypsinogen gene in miniature schnauzers with pancreatitis, but did find variations in the gene coding SPINK-1(Bishop et al. 2004; Bishop et al. 2010). However, a more recent study questioned the significance of this finding because SPINK-1 mutations were found in both miniature and standard schnauzers both with and without pancreatitis (Furrow et al. 2012).

Cystic fibrosis is not recognized in dogs and cats but it is possible that functionally milder mutations in the CFTR play a role in susceptibility to pancreatitis in dogs. A recent study screened for CFTR mutations in 174 supposed healthy dogs, 203 dogs with supposed pancreatitis and 23 dogs with bronchiectasis (Spadafora et al. 2010). A number of CFTR variants were found in dogs at least one of which is associated with an increased risk of pancreatitis in humans. Dogs with pancreatitis did not have a significantly higher prevalence of these variants than the healthy or 'normal' control dogs in this study. However, the diagnoses of either pancreatitis or 'normal' were not robust and there could have been significant phenotypic crossover between the groups. The question therefore remains unanswered as to whether CFTR variants predispose to pancreatitis in dogs.

Hypertriglyceridaemia is a recognised cause of recurrent acute pancreatitis in both humans (Tsuang et al. 2009) and dogs (Xenoulis & Steiner 2010). In dogs, it is most commonly reported in miniature schnauzers (Xenoulis et al. 2010). The pathogenesis of hypertriglyceridaemia-induced pancreatitis is poorly understood. It is postulated that pancreatic lipase might break down triglycerides to fatty acids within the pancreas resulting in acinar damage

(Tsuang et al. 2009). An alternative theory suggests that hyperviscosity of the blood compromises pancreatic oxygen supply (Tsuang et al. 2009). However, interestingly, although there is a recognised threshold blood concentration of triglycerides which will predispose to pancreatitis in humans, there is no correlation above that threshold between the concentration of triglycerides and the severity of pancreatitis, which perhaps argues against both of these proposed mechanisms (Talukdar & Vege 2009).

Hypercalcaemia should increase the risk of pancreatitis, but only if this high extracellular calcium is reflected in high intracellular or at least ductular calcium concentrations. In fact, hypercalcaemia seems to be more of a risk factor for acute pancreatitis in cats than in dogs and the reason for this species difference is unknown (Frick et al. 1990; Berger & Feldman 1987).

Alcohol and smoking are common contributing causes of CP in humans, when combined with genetic risk factors (Talukdar & Vege 2009). Other toxins and drugs can also cause pancreatitis. In humans, at least 120 drugs have been associated with acute pancreatitis (Talukdar & Vege 2009). Drugs reported to cause pancreatitis in dogs and cats include: azathioprine (Moriello et al. 1987); potassium bromide with phenobarbitone (Gaskill & Cribb 2000); organophosphates (Frick et al. 1987); asparaginase (Stephanie E Schleis 2011; Teske et al. 1990); sulphonamides (Trepanier 2004); zinc (Mikszewski et al. 2003; Blundell & Adam 2013) and clomipramine (Kook et al. 2009). Large studies are necessary to have the statistical power to prove or disprove drug toxicity and these are not usually available in veterinary medicine. For

example, asparaginase has long been accepted as causing pancreatitis in dogs (Teske et al. 1990; Schleis 2011) but a recent (small) study questioned this (Wright et al. 2009) . However, if drugs interact with genetic susceptibilities, large numbers of dogs of various breeds will need to be investigated before drug toxicity can be confidently excluded.

Duct blockage might be expected to increase the risk of pancreatitis particularly if associated with increased stimulation of enzyme release as may occur with increased autonomic or hormonal (chymotrypsin) stimulation or a change in pH of the ductular fluid. Duct ligation is commonly used in experimental canine models of CP. It is possible to produce lesions of CP in this species by pancreatic ligation with partial duct obstruction (Nagaya et al. 2004); direct pancreatic duct ligation (Hayakawa et al. 1993); alcohol administration combined with duct ligation (Tanaka et al. 1998) and pancreatic duct occlusion with prolamine (Meister et al. 1991) or neoprene or polyisoprene (Gooszen et al. 1984). However, the importance of duct blockage in naturally occurring canine CP is unknown. Gall stones are a common cause of acute pancreatitis in humans when stones become lodged at the Sphincter of Oddi, blocking both the pancreatic and bile ducts just before they enter the duodenum (Lowenfels et al. 2009; van Geenen et al. 2010). In most cats, but not dogs, the pancreatic and bile duct join before entering the duodenum making this a potential cause of feline acute pancreatitis. Gall stones are recognized in cats but are uncommon and their contribution to pancreatitis in this species is unknown (Gaillot et al. 2007; Eich & Ludwig 2002). Sphincter of Oddi dysfunction, where blockage or spasm of

573 the sphincter causes intermittent blockage, has been reported in a small
574 number of cats (Furneaux 2010) and could cause pancreatitis in some cats,
575 although further studies are necessary to confirm this.
576
577 The pancreas is very sensitive to ischaemia and any condition resulting in
578 pancreatic ischaemia can cause pancreatitis. Pancreatic ischaemia has been
579 used to produce an experimental model of CP in dogs (Tanaka et al. 1994).
580 Ischaemia is a rare but recognized cause of acute pancreatitis in humans, for
581 example after cardiac surgery (Lonardo et al. 1999). Haemolysis, both
582 autoimmune and associated with haemodialysis, also causes pancreatitis in
583 humans, in up to 20% of cases if it is severe (Abtahi et al. 2007; Druml et al.
584 1991).The association between haemolysis and other forms of ischaemia and
585 clinical acute pancreatitis in dogs is suspected but less well documented. One
586 unpublished study documented raised serum pancreatic lipase
587 immunoreactivity but no clinical signs of pancreatitis in four out of ten dogs
588 with immune-mediated haemolytic anaemia (Warman et al 2008). Pancreatitis
589 is a recognized complication of canine babesiosis in which the
590 pathophysiology may be at least partly due to haemolysis (Möhr et al. 2000).
591 Acute pancreatitis can be induced experimentally by injection of
592 cholecystokinin in dogs (Simpson et al. 1995) but the role of overstimulation in
593 naturally occurring pancreatitis in dogs is unknown.
594
595 Autoimmune CP is a distinctive form of CP described in humans, associated
596 with infiltration of T lymphocytes focused on pancreatic ducts and veins (Dite
597 et al. 2008). The most recent classifications divide autoimmune CP in to two

598 types (Deshpande et al. 2012). Type 1, the most commonly recognized, is a
599 multisystemic disease affecting kidney, liver, tear ducts and other organs as
600 well as the pancreas. This form is associated with elevation in serum IgG4
601 levels and increased IgG4-expressing plasma cells within the lesions and is
602 now termed 'IgG4 related disease' (Bateman & Deheragoda 2009;
603 Deshpande et al. 2012). Type 2 autoimmune pancreatitis is more
604 controversial, is confined to the pancreas with or without gut involvement and
605 shows no association with IgG4. IgG4 is one of 4 subtypes of IgG (types 1, 2,
606 3 and 4) which are recognized in humans and also in dogs (Day et al. 1996;
607 Day & Mazza 1995). The serum and tissue concentrations in healthy
608 individuals of both species usually decrease in numerical order, with IgG1
609 being the most abundant and IgG4 the least abundant.
610
611 English cocker spaniels suffer from a distinctive form of CP which shows
612 similarities to human type 1 autoimmune CP. Affected dogs demonstrate duct-
613 centred infiltrates of T-lymphocytes and also often have other immune-
614 mediated diseases such as keratoconjunctivitis sicca (Watson et al. 2011). A
615 predominance of IgG4+ plasma cells has been demonstrated in pancreatic
616 and renal histology in a small number of affected cocker spaniels (Watson et
617 al 2010) suggesting a remarkable similarity to the human disease. In addition,
618 CP in the English cocker spaniel is associated with an increased prevalence
619 of the same DLA haplotype as autoimmune haemolytic anaemia in the breed,
620 adding support for the theory of a polysystemic immune-mediated disease
621 (Bazelle et al 2013). However, it remains unproven that the cocker disease is

autoimmune and more studies on greater numbers of dogs, including response to immunosuppressive treatments, will be required to confirm this.

Conclusion

Pancreatitis is a common disease in both dogs and cats with potentially very serious consequences for the animal. However, in spite of this, there are very few studies on the causes (both genetic and environmental) and on the pathophysiology of the naturally occurring disease in small animals. This contrasts with the large number of studies in humans which have greatly increased understanding of the disease. Dogs and cats with pancreatitis do not always behave like humans: for example, small animals suffer from less infective complications and have different expressions of receptors in their pancreatic duct. Many more studies are therefore needed in small animals to enable more effective treatment and to help prevent the disease in the future. The ability in small animals to feed specific diets and breed selectively on the basis of genetic tests should confer an advantage in disease prevention, if understanding of the environmental and genetic risk factors could be increased.

647 Figure legends

648

649 Figure 1: Feline pancreas at surgery – right (duodenal) limb. Photo
650 acknowledgements to follow blind review

651

652 Figure 2: Histological section from the same cat as figure 1, showing typical
653 chronic pancreatitis: there are large bands of fibrous tissue (light pink)
654 separating islands of remaining acinar tissue (purple) and dense patches of
655 lymphocytes. Haematoxylin and eosin stain x 10.

656

657 Figure 3: diagrammatic representation of relationship between acute and
658 chronic pancreatitis. Arrows represent potential disease outcomes and
659 progression. Movement between boxes along arrows depends on interaction
660 of genes and environment in the individual. See text for more details.

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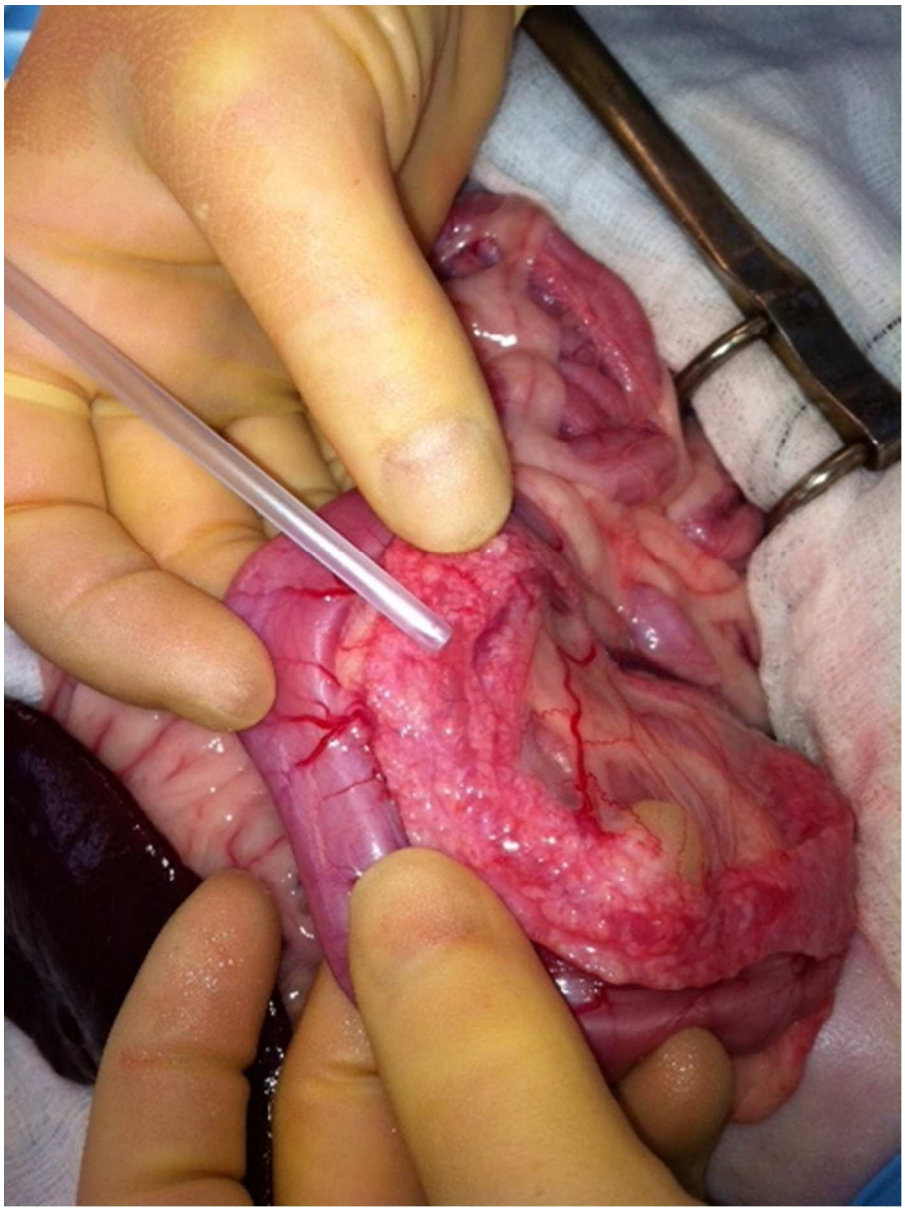
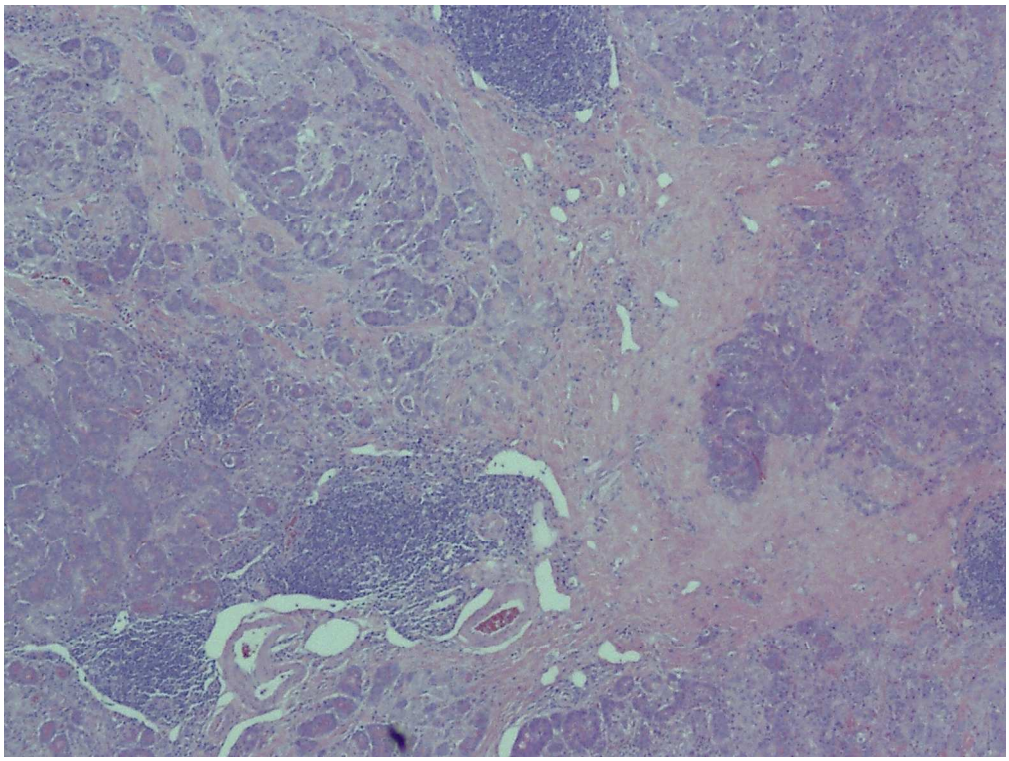
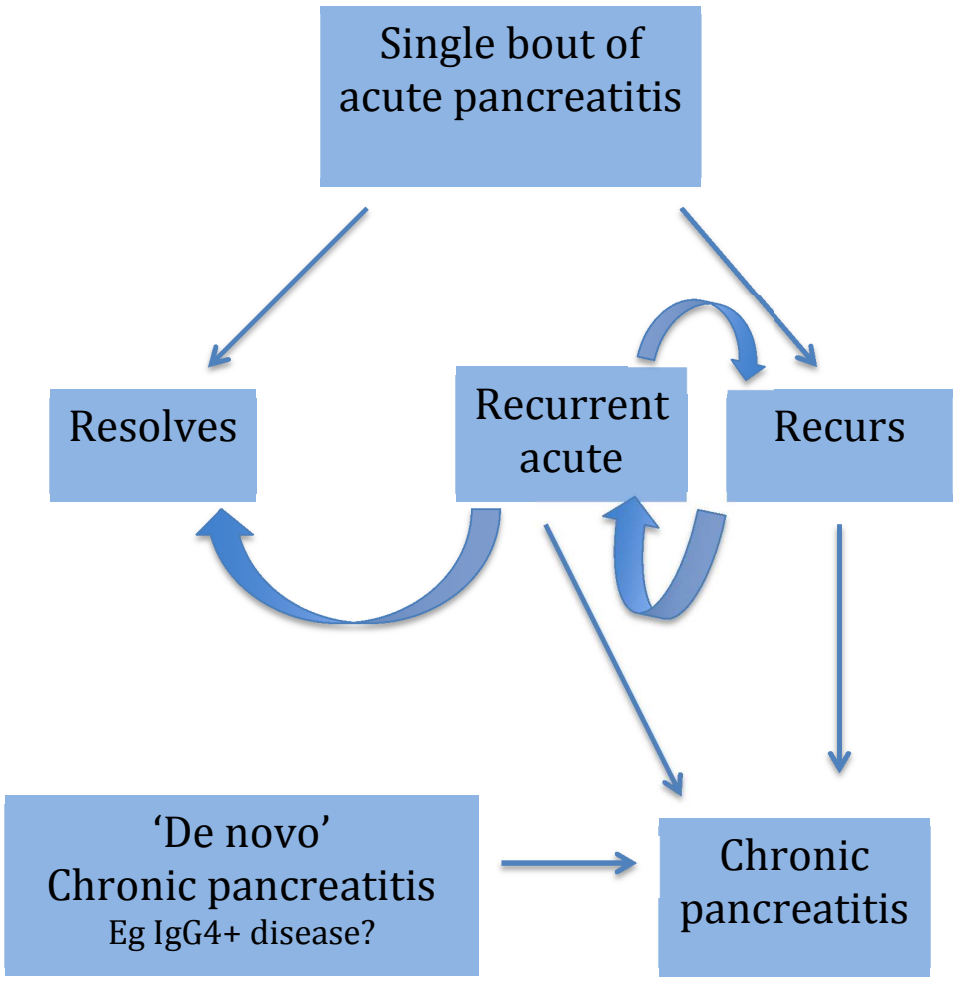


Feline pancreas at surgery – right (duodenal) limb. Photo acknowledgements to follow blind review
168x225mm (72 x 72 DPI)



Histological section from the same cat as figure 1, showing typical chronic pancreatitis: there are large bands of fibrous tissue (light pink) separating islands of remaining acinar tissue (purple) and dense patches of lymphocytes. Haematoxylin and eosin stain x 10.
564x423mm (72 x 72 DPI)

Figure 3


Single bout of acute pancreatitis
Resolves
Recurrent acute
Recurs
'De novo' Chronic pancreatitis
Eg IgG4+ disease?
Chronic pancreatitis