

1 **Summary**

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

17

18 **Structure of the normal canine and feline pancreas**

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

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

34

35 The exocrine acini comprise about 98% of the pancreatic mass in dogs and
36 humans (Evans 1993; Motta et al. 1997). The endocrine islets comprise about
37 2% of pancreatic mass (Evans 1993). The acini are linked via a series of
38 smaller ducts to two larger pancreatic ducts in most dogs: the larger duct is
39 actually the accessory duct in dogs, which enters the duodenum at the minor
40 duodenal papilla. The smaller duct is the pancreatic duct which enters the
41 duodenum approximately 28mm cranial to the accessory duct and in close
42 proximity to the bile duct at the major duodenal papilla (Evans 1993). The
43 pancreatic ducts in most dogs do not join the bile duct before exiting in to the
44 duodenum (Evans 1993). This anatomical arrangement differs from cats and
45 humans where the pancreatic duct usually joins the common bile duct just
46 before entering the duodenum at the Ampulla of Vater (Evans 1993; Lack
47 2003). A secondary minor, or accessory, pancreatic duct enters the
48 duodenum separately in humans and about 20% of cats, although many cats
49 do not have a second duct. Other anatomical variations exist in dogs but are
50 uncommon: for example, some dogs have only one pancreatic duct and in

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

53

54 **Definitions of acute and chronic pancreatitis:**

55 **a) Histological definitions**

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

67

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

76 features differentiating chronic from acute and recurrent acute pancreatitis are
77 permanent, irreversible and typically progressive histopathological changes,
78 particularly fibrosis and acinar loss as reported in humans (Etemad &
79 Whitcomb 2001a; Lack 2003). These changes are also recognized and
80 reported in dogs (Watson et al. 2007; Bostrom et al. 2013; Newman et al.
81 2006) and cats with CP (De Cock et al. 2007). The inflammatory cell infiltrate
82 in CP can be mononuclear or mixed mononuclear and granulocytic. In
83 humans, CP is very commonly associated with pancreatic ductular
84 concretions and calcifications (stones) (Lack 2003; Etemad & Whitcomb
85 2001b). These pancreatic ductular stones are very rarely recognized in dogs
86 and cats, although the reason for this is not known. Dogs have been shown to
87 secrete what is known as 'pancreatic stone protein' into their pancreatic ducts
88 but, unlike in humans, this does not precipitate in to stones (Bernard et al.
89 1991).

90

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

101 1998) and have considered that the presence on histology of pancreatic cell
102 necrosis and/or a neutrophilic infiltrate is the hallmark of 'acute' disease,
103 regardless of the potential concurrent presence of fibrosis and permanent
104 pancreatic architectural changes. In a case-control study of fatal acute
105 pancreatitis in dogs with histological confirmation involving 70 cases and 104
106 controls (Hess et al. 1998), 40% of the cases actually had acute pancreatic
107 necrosis superimposed on fibrosis i.e. acute-on-chronic disease. In addition,
108 statistical analysis showed that dogs in that study with fatal acute pancreatitis
109 had significantly more historical evidence of prior gastrointestinal disease
110 before their fatal bout than the control population of dogs, again supporting
111 the suggestion of previous ongoing CP in many of the dogs (Hess et al.
112 1999). The question remains as to whether these previous gastrointestinal
113 signs were due to CP, chronic enteritis or another disease. It is unknown
114 whether there is a relationship between CP and small intestinal disease in
115 dogs. An association between CP and enteritis has been described in cats
116 (Weiss et al. 1996), although the reason remains unclear.

117

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

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

135

136 ***Veterinary histological scoring schemes***

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

141

142 Two recent pathology studies of pancreatic lesions in dogs favour the human
143 definition of chronicity and classed all dogs with fibrosis as CP, even if they
144 had superimposed acute inflammation (Newman et al. 2004; Watson et al.
145 2007). A follow-up study by Newman et al (2006) suggested a histological
146 grading system for canine pancreatitis in which a number of histological
147 features were graded on each histological section between 0 and 3 where
148 grade 0 = none of the section affected; grade 1 was up to 10% of the section
149 affected; grade 2 was 10-40% of the section affected and grade 3 was over
150 40% of the section affected. The histological features graded were:

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

156

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

169

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

176

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

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

196

197 *The Atlanta classification of human acute pancreatitis*

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

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

220

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

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

228

229 *Non-invasive diagnostic criteria for human chronic pancreatitis*

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

246

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

251 standard in Europe for the diagnosis of CP and more recent classifications
252 have attempted to add to this with more details of history and function tests,
253 together with the incorporation of the newer diagnostic imaging methods of
254 endoscopic ultrasound and magnetic resonance cholangiopancreatography or
255 more clinically relevant sub-groups (Etemad & Whitcomb 2001b; Büchler et al.
256 2009; Bagul & Siriwardena 2006) The Japanese Pancreas Society developed
257 their own, slightly different, criteria in parallel in 1995 with updates in 2001
258 and 2010 (Shimosegawa et al. 2010). The difficulty with all these non-invasive
259 scoring schemes for human CP is the fact that they are much more likely to
260 give a diagnosis in more severe and more end-stage disease whereas
261 diagnosis of early CP with less marked functional and structural changes
262 remains a challenge.

263

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

266 An important addendum to the discussion of functional changes with CP is to
267 stress the importance in dogs of differentiating pancreatic acinar atrophy
268 (PAA) from end stage CP as causes of EPI. There has been occasional
269 confusion in the literature suggesting they are the same disease (Sutton
270 2005). However, they are clinically and histologically very distinctive. PAA is
271 particularly recognized in young German shepherd dogs (GSDs), but also
272 rough collies, English setters and sporadically in other breeds (Westermarck
273 & Wiberg 2003; Westermarck & Pamilo 1989; German 2012). In GSDs with
274 PAA, an autosomal mode of inheritance has been suggested (Westermarck
275 1980) although a recent study refutes this and suggests the inheritance is

276 more complex (Westermarck et al. 2010)

277 Histological studies in GSDs suggest that PAA is an autoimmune disease
278 directed specifically against the acini (Wiberg et al. 2000). Therefore the islets
279 are spared, and dogs with PAA are not typically diabetic. However, affected
280 dogs do not respond to immunosuppressive therapy (Wiberg & Westermarck
281 2002). Most dogs develop the disease in young adulthood, but a proportion of
282 GSDs remain subclinical for a prolonged period of time and present only late
283 in life (Wiberg & Westermarck 2002). Importantly, the predominant histological
284 change is pancreatic acinar atrophy with replacement of acinar tissue with fat,
285 while islets remain – PAA is NOT characterised by pancreatic fibrosis and
286 inflammatory cells are only seen in the early stages of the disease.

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

299

300 **Pathophysiology of acute and chronic pancreatitis in dogs and cats**

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

308

309 *Interaction between genes and environment*

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

321

322 *Relationship between acute and chronic disease*

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

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

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

340

341 *Over-view of pathophysiology of acute pancreatitis*

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

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

355

356 Recent studies in humans stress the importance of a compensatory anti-
357 inflammatory response (known as CARS) in localising the inflammation to the
358 pancreas and preventing systemic dissemination (Talukdar & Swaroop Vege
359 2011; Kylänpää et al. 2012). Mild acute pancreatitis is associated with CARS
360 which is characterised by up regulation of anti-inflammatory cytokines such as
361 IL10 and 11 (Kylänpää et al. 2012). It is suggested in humans that an
362 excessive CARS may suppress the immune system enough to predispose to
363 bacterial or fungal infection of pancreatitis necrosis, which is a relatively
364 common and serious sequela to pancreatitis in humans. (Kylänpää et al.
365 2012; Talukdar & Swaroop Vege 2011). In contrast, infected necrosis is very
366 rare in dogs and cats although it is occasionally reported (Marchevsky et al.
367 2000).

368

369 The pro-inflammatory response in pancreatitis in humans and rodents is
370 characterised by generalised activation of proinflammatory cytokines such as
371 the inducible transcription factor NF- κ B; TNF α and IL 6 and 8.(Kylänpää et al.
372 2012). A study in dogs also showed elevation in TNF α in plasma in 31%
373 dogs with severe acute pancreatitis (Ruaux et al. 1999). These cytokines lead
374 to generalised neutrophil and monocyte activation resulting in damage to

375 vascular endothelium throughout the body, with ensuing tissue oedema and
376 hypoxia. Organs with extensive capillary beds such as the lungs, kidneys and
377 liver are particularly susceptible to damage (Talukdar & Swaroop Vege 2011).
378 The coagulation cascade may also be activated ultimately resulting in DIC in
379 some cases. IL 6 is a potent inducer of acute phase protein production in the
380 liver such as c-reactive protein (Kylänpää et al. 2012). Pancreatitis is
381 recognised as one of many diseases which results in increased c-reactive
382 protein concentrations in dogs (Nakamura et al. 2000). It is clearly recognised
383 in humans that mortality in severe acute pancreatitis is much more closely
384 related to this multi-organ failure than to the apparent severity of the
385 pancreatitis itself (Kylänpää et al. 2012; Talukdar & Vege 2009; Banks et al.
386 2012). Two studies also support this theory in naturally occurring pancreatitis
387 in dogs: in one study of 60 dogs with acute pancreatitis, TNF α was elevated
388 in 31% of dogs with severe disease and strongly associated with a lethal
389 disease outcome (Ruauux et al. 1999). In the same dogs, the concentration of
390 plasma α macroglobulin was found to be significantly reduced from normal,
391 consistent with its consumption clearing circulating proteases, but there was
392 no significant difference in α macroglobulin between severity groups (Ruauux &
393 Atwell 1999). Taken together, these findings suggest also that the severity of
394 the systemic inflammatory response is better correlated with outcome in dogs
395 than the release of proteases from the pancreas.

396

397 *Protection against trypsin activation*

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

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

414

415 An early breakthrough in the understanding of the pathogenesis of
416 pancreatitis in humans was the discovery of mutations in the cationic
417 trypsinogen gene which cause autosomal dominant hereditary pancreatitis
418 (Etemad & Whitcomb 2001b; LaRusch & Whitcomb 2011). About 20 gain-of-
419 function mutations in this gene have been identified in humans and they all
420 cluster around calcium-binding sites which regulate trypsin activation. Calcium
421 concentration is very low in acinar cells but high within the pancreatic duct
422 and small intestinal lumen, favouring trypsin activation (LaRusch & Whitcomb
423 2011). Activation of trypsin is also pH dependent: although trypsin requires a
424 relatively high pH to function (i.e the alkaline pH of the small intestine), its

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

438

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

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

451

452 Other mutations in humans which predispose to pancreatitis but only when
453 combined with other risk factors include a number of mutations in the cystic
454 fibrosis transmembrane conductance regulator (CFTR) which are not severe
455 enough to cause cystic fibrosis and mutations in the chymotrypsin C gene
456 (LaRusch & Whitcomb 2011). There is also increasing focus in human
457 medicine on the phenomenon of 'epistasis' whereby the effects of one gene
458 modify the effects of another. For example, the concurrence of variants of
459 SPNIK1 and CFTR can be synergistic (LaRusch & Whitcomb 2011). Severe
460 mutations of CFTR result in cystic fibrosis which is an important cause of CP
461 in humans because of duct blockage by the abnormal ductular secretion and
462 changes in pH and calcium concentrations in this fluid (Wilschanski & Novak
463 2013).

464

465 **Potential causes of acute and chronic pancreatitis in dogs.**

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

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

475

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

486

487 Study of genetic predispositions to pancreatitis in dogs is at a very early stage
488 and there are no studies to date in cats. It is very likely that genetic
489 predispositions exist in dogs because clinical studies show significant breed
490 prevalences: terriers have been reported to have an increased risk of acute
491 disease (Hess et al. 1999). CKCS, boxers, cocker spaniels and Border collies
492 appear to have an increased risk of chronic disease in the UK (Watson et al.
493 2007; Watson et al. 2010; Watson et al. 2011). In the USA, dogs classed by
494 the American Kennel Club as toy/non-sporting dogs appear to have an
495 increased risk of chronic disease (Bostrom et al. 2013). Studies of canine
496 mutations predisposing to acute pancreatitis have focussed on miniature
497 schnauzers. Studies in the USA have shown no mutations in the cationic

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

503

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

516

517 Hypertriglyceridaemia is a recognised cause of recurrent acute pancreatitis in
518 both humans (Tsuang et al. 2009) and dogs (Xenoulis & Steiner 2010). In
519 dogs, it is most commonly reported in miniature schnauzers (Xenoulis et al.
520 2010). The pathogenesis of hypertriglyceridaemia-induced pancreatitis is
521 poorly understood. It is postulated that pancreatic lipase might break down
522 triglycerides to fatty acids within the pancreas resulting in acinar damage

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

530

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

536

537 Alcohol and smoking are common contributing causes of CP in humans, when
538 combined with genetic risk factors (Talukdar & Vege 2009). Other toxins and
539 drugs can also cause pancreatitis. In humans, at least 120 drugs have been
540 associated with acute pancreatitis (Talukdar & Vege 2009). Drugs reported to
541 cause pancreatitis in dogs and cats include: azathioprine (Moriello et al.
542 1987); potassium bromide with phenobarbitone (Gaskill & Cribb 2000);
543 organophosphates (Frick et al. 1987); asparaginase (Stephanie E Schleis
544 2011; Teske et al. 1990); sulphonamides (Trepanier 2004); zinc (Mikszewski
545 et al. 2003; Blundell & Adam 2013) and clomipramine (Kook et al. 2009).
546 Large studies are necessary to have the statistical power to prove or disprove
547 drug toxicity and these are not usually available in veterinary medicine. For

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

553

554 Duct blockage might be expected to increase the risk of pancreatitis
555 particularly if associated with increased stimulation of enzyme release as may
556 occur with increased autonomic or hormonal (chymotrypsin) stimulation or a
557 change in pH of the ductular fluid. Duct ligation is commonly used in
558 experimental canine models of CP. It is possible to produce lesions of CP in
559 this species by pancreatic ligation with partial duct obstruction (Nagaya et al.
560 2004); direct pancreatic duct ligation (Hayakawa et al. 1993); alcohol
561 administration combined with duct ligation (Tanaka et al. 1998) and pancreatic
562 duct occlusion with prolamine (Meister et al. 1991) or neoprene or
563 polyisoprene (Gooszen et al. 1984). However, the importance of duct
564 blockage in naturally occurring canine CP is unknown. Gall stones are a
565 common cause of acute pancreatitis in humans when stones become lodged
566 at the Sphincter of Oddi, blocking both the pancreatic and bile ducts just
567 before they enter the duodenum (Lowenfels et al. 2009; van Geenen et al.
568 2010). In most cats, but not dogs, the pancreatic and bile duct join before
569 entering the duodenum making this a potential cause of feline acute
570 pancreatitis. Gall stones are recognized in cats but are uncommon and their
571 contribution to pancreatitis in this species is unknown (Gaillot et al. 2007; Eich
572 & 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

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

624

625 **Conclusion**

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

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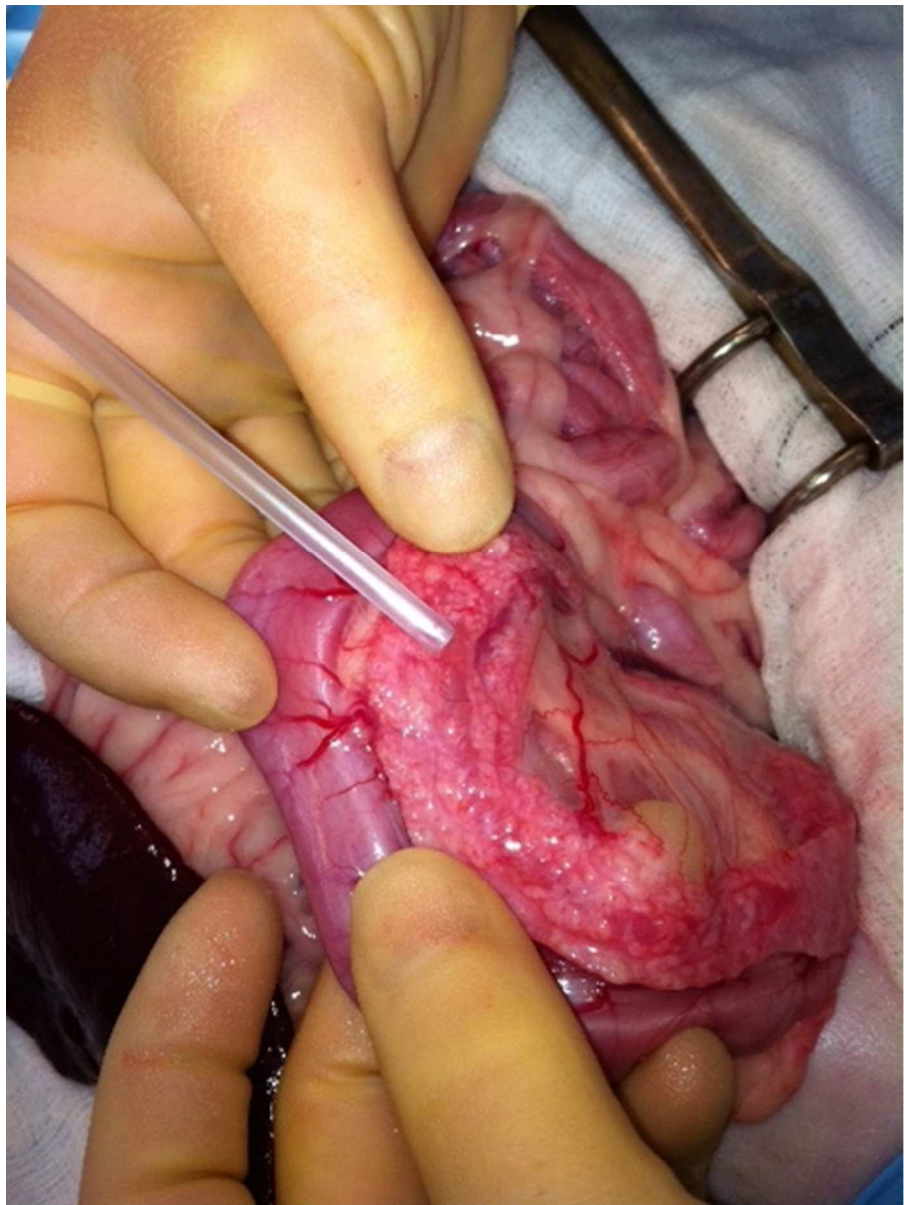
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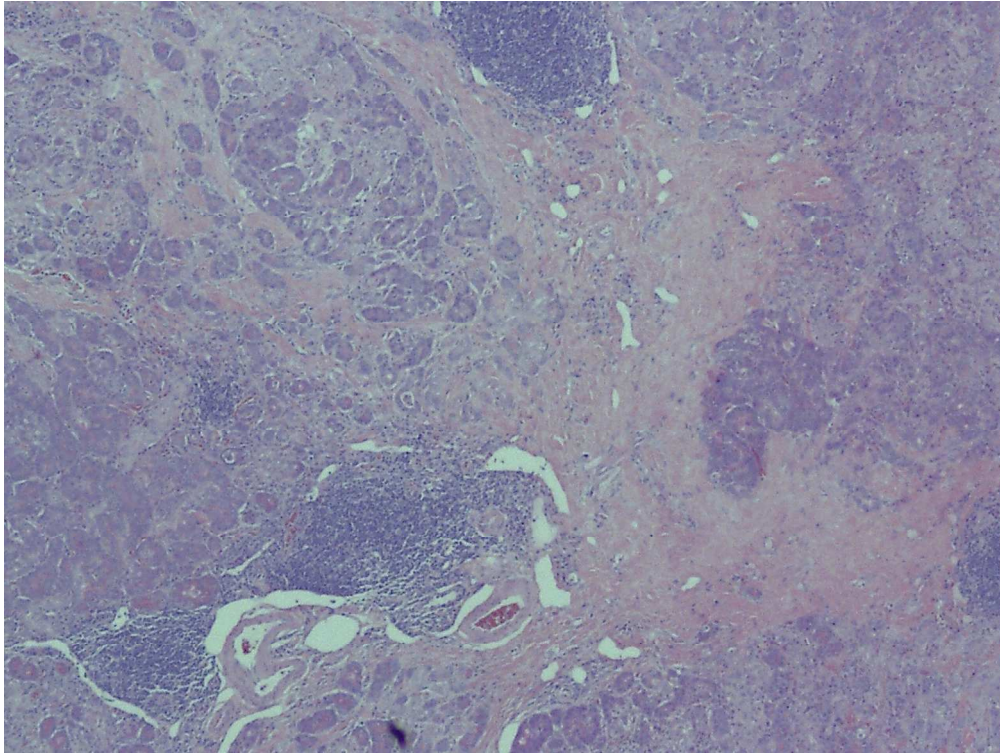
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Feline pancreas at surgery – right (duodenal) limb. Photo acknowledgements to follow blind review
168x225mm (72 x 72 DPI)



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

