Veterinary Bioscience: Digestive System

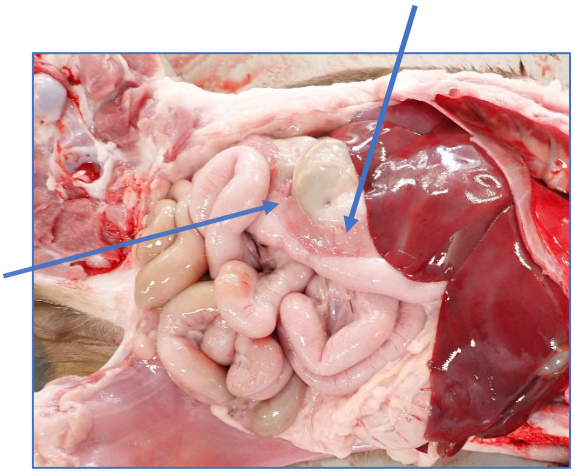
LECTURE 20
PATHOLOGY OF THE PANCREAS

LECTURER

DR ELIZABETH DOBSON

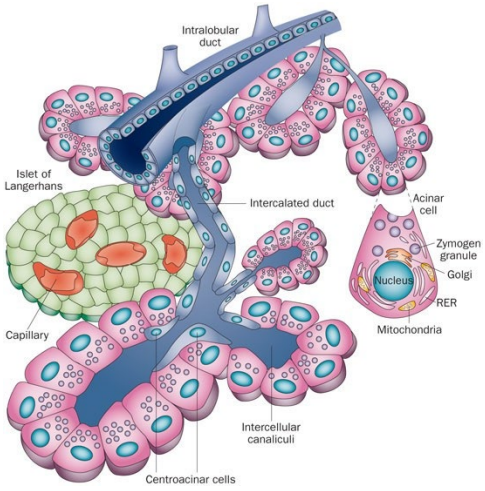
Liz.Dobson@unimelb.edu.au

Anatomy



The pancreas is a pale glandular tissue which runs along the mesenteric border of the proximal duodenum. It has a lobular architecture that varies between species. In dogs it extends along the cranial flexure of the duodenum within the mesoduodenum and extends over the caudal surface of the stomach.

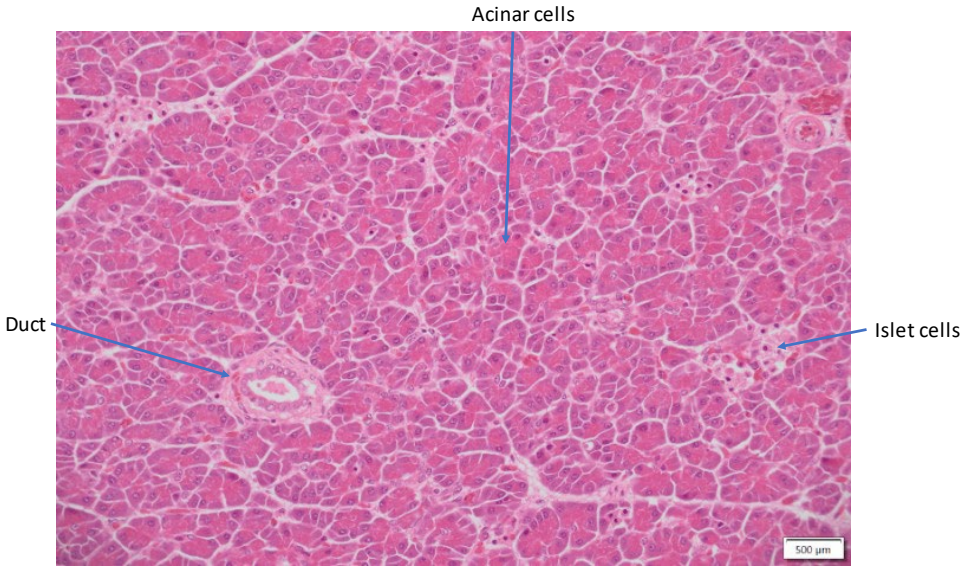
The pancreatic duct drains into the duodenum, often immediately adjacent to the bile duct. The location of the pancreatic duct/s varies between species. The bile duct also runs through the pancreas.



https://www.nature.com/articles/nrgastro.2013.36

Function

The pancreas has both endocrine and exocrine tissue. The function of the exocrine pancreas is of food digestion in the duodenum. The digestion of dietary protein is primarily by proteases, dietary carbohydrates by amylase and dietary fat by lipase in combination with bile salts.



Canine pancreas x10 H&E

Pancreatic secretion is initiated by 4 different mechanisms:

1. Sensory inputs (cephalic phase),
2. Entry of food into the stomach (gastric phase),
3. Movement of acid digesta into the duodenum (**intestinal phase**) and
4. nutrient absorption from the intestinal lumen (absorbed nutrient phase).

Both functional and structural changes occur in response to systemic metabolic activity. Function is regulated by entero-endocrine hormones derived from the gastrointestinal mucosa and from the endocrine component of the pancreas.

Intestinal phase

Entry of gastric acid and fatty acid into duodenum

Release of secreting and release of **cholecystokinin** by mucosal endocrine cells

Secretion of water and bicarbonate by ductal epithelium & release of digestive enzymes from zymogen granules into ducts

Key functions of the exocrine pancreas:

- Synthesis and secretion of digestive enzymes
- Acinar cells
    - synthesise trypsin, chymotrypsin, collagenase, phospholipase, elastases and carboxypeptidases as inactive proenzymes
    - synthesise amylase and lipase in their active forms which are present in the cytoplasm within membrane-bound zymogen granules

The formation of inactive proenzymes and active enzymes within membrane-bound granules protects the tissue from auto-digestion.

Pancreatic enzymes also digest the glycoprotein carrier of intrinsic factor enabling it to bind to Vitamin B12 which is essential for its absorption in the ileum

Pancreatic secretions are adaptable to changes in nutrition. Changes in diet will result in alterations to the composition of pancreatic secretions.

The exocrine pancreas begins to function/synthesize enzymes a few weeks after birth. At weaning there is a significant change in the pattern of enzyme secretion associated with dietary and hormonal changes

The pancreas has significant regenerative capacity following damage. Remaining acinar cells can proliferate by mitotic division or is damage is severe, ductular cells can proliferate and differentiated into ductular epithelium, acinar cells or islet cells.

Pathology

Acute Pancreatic Necrosis

This is a commonly encountered disease in domestic animal practice that generally requires rapid medical intervention. The presenting clinical signs in dogs are variable and can include acute onset, persistent vomiting, haemorrhagic diarrhea and jaundice or vague abdominal pain. Occasional cases can progress to shock and death. Some cases can be subclinical and go undetected until exocrine pancreatic insufficiency or diabetes mellitus emerge. The condition is more difficult to diagnose in cats who often present with non-specific signs.

Pathogenesis

The tissue necrosis develops associated with local release of active pancreatic enzymes. Fusion of zymogen granules with lysosomes in acinar cells triggers activation of trypsinogen which, in turn, activates other pancreatic enzymes. The fusion of the zymogen granules with lysosomes is induced by a sustained rise in the intracellular isonised calcium concentration.

Factors implicated as causes of acute pancreatic necrosis:

- Hyperlipidemic conditions:

  Obesity, high fat, low protein diets, ingestion of a large, fatty meal, idiopathic hyperlipidemia of miniature schnauzers, hyperadrenocorticism

- Pancreatic hypoxia:

  Reduced oxygen levels leads to dysregulation of intracellular calcium stores. This can be induced by hypovolemia, hypotension, local vasoconstriction, disseminated intravascular coagulation, pancreatic trauma and abdominal trauma

- Conditions causing systemic hypercalcemia:

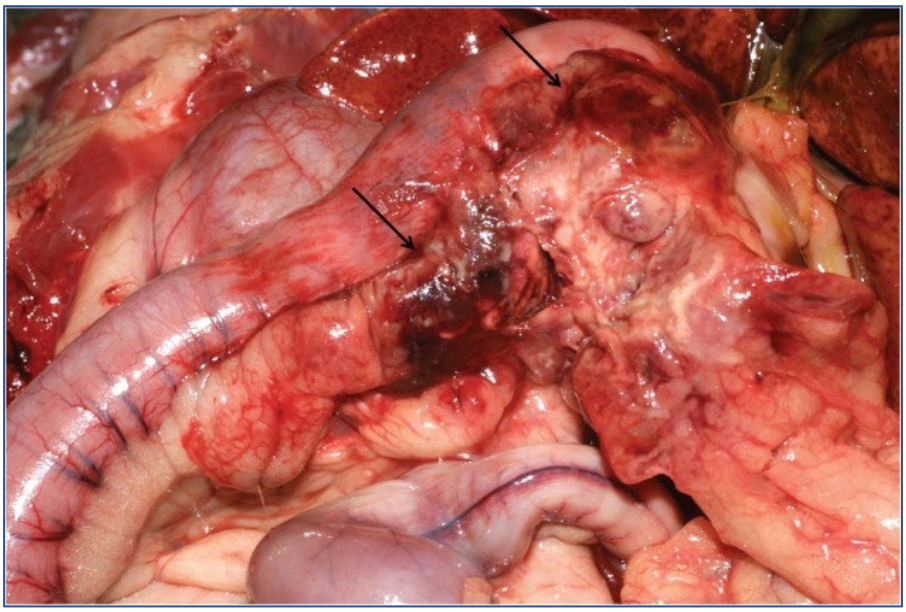
  This also leads to increased intracellular calcium. Primary causes are renal failure and paraneoplasic hypercalcemia (esp. lymphoma)

- Drugs and toxins:

  Corticoseroids, azothiaprine and scorpion envenomation

The activated pancreatic enzymes cause local tissue damage and vascular injury. The vascular injury contributes via increased permeability, oedema, haemorrhage, local thrombosis and further tissue ischemic necrosis. Oxygen-derived free radicals from vascular injury and hypoxia further contribute to tissue damage.

Consumption of serum protease inhibitors activates the kinin, coagulation, fibrinolytic and complement cascade leading to vasodilation, hypotension, shock and disseminated intravascular coagulation. These events can culminate in multiple organ failure and death.



Watson, P. Journal of Small Animal Practice (2015) 56, 3–12 DOI: 10.1111/jsap.12293

Clinical Pathology

Haematology and serum biochemistry results are non-specific and can be normal, particularly in mild cases. Classically dogs will have a neutrophilia (possibly left shifted) and an elevation in C-reactive protein however significant variations can be seen.

Biochemistry changes can include significant elevations in amylase and lipase however they have poor sensitivity and specificity. Elevations greater than 3-5x the upper limit of the reference interval should be considered significant. Both amylase and lipase are also synthesised in the gastrointestinal tract and liver so elevations can be associated with tissue damage elsewhere. Canine and feline pancreatic specific lipase is considered more sensitive and specific however the sensitivity drops significantly with mild disease. Liver enzymes (AlkP, ALT) can be elevated and there can be hyperbilirubinemia. Other possible findings include hypoalbuminaemia, hypertriglyceridaemia, hypercholesterolaemia; both elevated and decreased glucose are possible. The most common electrolyte changes are hypokalemia, hypochloremia and hyponatremia. Hypocalcemia can be seen in cats. Occasional cases can have increased clotting times. Dogs can develop DIC due to activation of clotting factors with widespread endothelial cell damage

Pathology

Grossly the peripancreatic adipose is necrotic and develops a chalky appearance often with associated haemorrhage. Often there is an effusion occasionally with free lipid droplets. The pancreas is thickened and nodular and often dark red to black. Chronic pancreatitis cases are often small and fibrotic.

Histologically there is necrosis and inflammation dominated by neutrophils often at the periphery of lobules. This can be multifocal or regionally extensive. Acinar cell damage starts with microvesicular degeneration and progresses to necrosis. In chronic disease there is acinar atrophy and fibrosis

A reported associated condition is multifocal necrotising panniculitis which is thought to be associated with release of enzymes into circulation. Other possible sequale to primary pancreatitis include paralytic ileus, extrahepatic bile duct obstruction or duodenal obstruction. Pancreatitis is generally a sterile condition however secondary ascending infections rarely occurs by enteric bacteria.

Individual acinar cell necrosis or small groups of cells associated can occur secondary to a wide variety of systemic disease, shock, toxins and epitheliotropic viral infections (adenoviruses, distemper, FMD).

Exocrine pancreatic insufficiency (EPI)

Exocrine pancreatic insufficiency is a condition characterised by a deficiency in pancreatic enzymes leading to maldigestion and malabsorption. This is typically seen with significant loss of exocrine pancreatic tissue and can develop as congenital or acquired disease. Due to the large functional reserve of the exocrine pancreas, this disease only develops once >90% of secretory function is lost.

EPI is most common in dogs and is often associated with juvenile pancreatic atrophy; German shepherds, Rough coated collies, Chows, English setters, greyhounds & beagles are predisposed. Most cases have clinical signs by 6-12 months of age. These cases have intense but patchy infiltration of T lymphocytes (atrophic lymphocytic pancreatitis). The nature of the inflammation

suggests it is autoimmune disease although not proven. The Islet cells are usually normal however some greyhounds lose both and develop diabetes mellitus.

In cats it is most commonly associated with chronic, subclinical pancreatitis in older animals.

Clinically animals present in low body condition with voluminous, soft faeces, steatorrhea, hepatic steatosis and often develop pica or coprophagia.

Clinical pathology

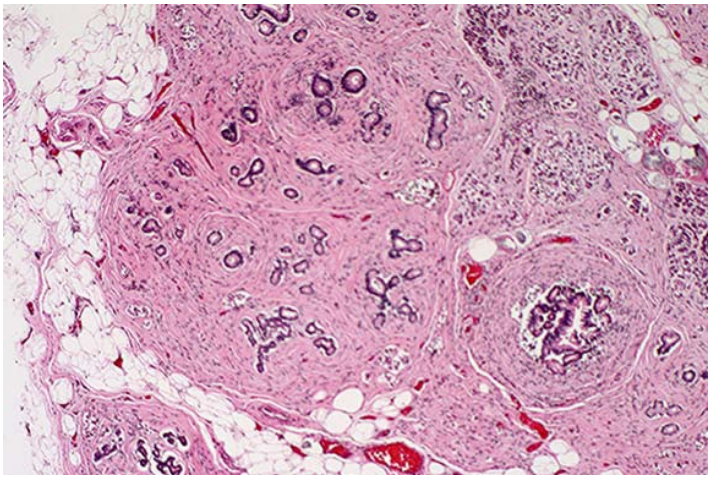
Measurement of serum trypsin-like immunoreactivity is the most useful screening tool. Routine haematology and biochemistry can be normal. Some animals can develop specific nutrient deficiencies secondary to malabsorption including vitamins B12 (cobalamin), A, D and E. Occasionally affected animals can develop clotting deficiencies because of malabsorption of fat-soluble vitamin K.

Malassimilation of nutrients is multifactorial. The change to the intestinal luminal microenvironment can lead to atrophy of intestinal villi, disruption of intestinal transport mechanisms and change to the luminal flora. Small intestinal bacterial overgrowth can occur (dysbiosis) although this can be difficult to characterise as they are often commensals; a bacterial count can be useful diagnostically.

Pathology

Cases of congenital atrophy have significant decrease in pancreatic tissue.

Westermark, E and Wiberg, M. (2012) http://dx.doi.org/10.1053/j.tcam.2012.05.002



https://www.askjpc.org/wsco/wsc/wsc97/97wsc11.htm

Chronic interstitial pancreatitis

This condition develops as an extension of chronic inflammation initially around the pancreatic ducts. It is thought to arise from an ascending infection (+/- cholangitis) or ductular parasites (eg *Strongylus equinus* in horses or fluke migration). There is often extensive scar tissue combined with pancreatic atrophy and compensatory nodular hyperplasia. The common biliary and pancreatic drainage in cats and horses means the pancreas is susceptible to extension from primary cholangitis. Cats can present with triaditis where there is concurrent inflammation in the duodenum, biliary tree (+/- liver) and pancreas.

Pancreatic hyperplasia and neoplasia

- Exocrine hyperplasia
  This condition is common in older animals and is seen as variably sized dispersed nodules throughout the pancreas. It is considered an incidental finding. Histologically there is no distinct capsule around the nodules and there is no damage to the surrounding tissue
- Ductular hyperplasia
  This change is often seen secondary to other underlying pancreatic disease. It can also be seen as an aging change
- Exocrine pancreatic adenomas
  Adenomas of the pancreas are uncommon and are easily confused with hyperplastic nodules. They are considered incidental; to date there is no evidence they transform into adenocarcinoma. These masses have expansile growth which compresses the adjacent parenchyma and are typically enclosed within a thin capsule. They are most commonly in a tubular pattern arising from the pancreatic ducts or and acinar pattern arising from exocrine cells
- Exocrine pancreatic adenocarcinoma
  Adenocarcinomas are also uncommon tumours in domestic animals; when present they are generally (not always) seen in older aged animals. There is a possible link with nitrosamines (nitrite preservatives), chronic pancreatitis & diabetes mellitus. Some animals can develop secondary pancreatic panniculitis and cats can develop paraneoplastic alopecia.
  Adenocarcinomas can be a single mass or multiple masses throughout the pancreas. They are usually firm with necrosis and haemorrhage on cut section. Microscopically there are tubular, acinar and hyalinising forms or can be anaplastic. These are aggressive tumours that metastasise widely but are also locally aggressive with invasion into intestinal wall and peritoneal implantation. Obstruction of the pancreatic and bile ducts can occur. Extends along visceral nerves to dorsal ganglia
  The common sites of metastasis are liver, lungs and regional lymph nodes but metastasis can be widespread to other viscera.

Exocrine atrophy

- Typically associated with nutrient deprivation – starvation, prolonged anorexia, cachexia, protein-caloric deficiency and maldigestive-malabsorptive syndromes
  - Catabolic loss of acinar cells to compensate for nutritional shortfall + loss of hormonal and neurogenic stimulation
- Selenium deficiency +/- Vit E deficiency → depletion of glutathione peroxidase and oxidative damage

- Depletion of zinc, copper, Vit A and essential amino acids
- Obstruction of ductal drainage (parasites, inflammation ,neoplasia, pancreoliths)

Developmental abnormalies

- Agenesis or aplasia (complete absence)
  - Incompatible with survival
- Hypoplasia of exocrine tissue
  - Occasionally seen in calves
- Congenital stenosis or cystic dilation of the duct
  - Can be accompanied by polycystic kidneys and bile duct cysts
- Ectopic pancreatic tissue
  - Intestinal or gastric wall, liver, spleen, mesentery etc

Zinc toxicity

- Alloys, galvanised products, pesticides, herbicides, zinc salts
- Consistent lesion in pancreas, liver, kidney and blood (Heinz body haemolytic anaemia)
- Pancreas is major route of zinc excretion

Parasitic disease

- Migrating larvae (eg. Strongyles in horses)
- Pancreatic ducts – significance depends on the degree of occlusion
  - Heavy infestations of intestinal parasites can invade the duct from the intestine
  - Thysanoma actinoides (tapeworm) normally in bile ducts can extend into pancreatic duct and intestinal lumen
  - Eutrema flukes can inhabit both the pancreatic and bile ducts

Extra Reading

Head. K.W. et al. (2017). 'Tumors of the Alimentary Tract' in Meuten, D.J. (ed.) *Tumors of Domestic Animals*. Ames, Iowa:Wiley, pp 203-321
Jubb. K.W. et al. (2016). 'Pancreas in Maxie, G.A. (ed.) *Pathology of Domestic Animals*. Missouri:Elsevier, pp 353-373.