Comparative Pancreatic Pathology

EM Whitley, Iowa State University, Ames, IA, USA

Glossary

Acinus (plural, acini; adjective, acinar) A cluster of cells composing the smallest unit of a compound gland. In the pancreas, these cells are the site of production of precursor digestive enzymes.

Adenocarcinoma A malignant neoplasm arising in the glandular epithelial cells. Cells are arranged in acinar or duct-like patterns, reminiscent of glands.

Adenoma A benign neoplasm arising in the epithelial cells.

Carcinoma A malignant neoplasm arising in the epithelial cells.

Endocrine Glands that secrete hormones directly into the bloodstream.

Exocrine Glands that deliver secretory products via a duct system.

Hyperglycemia Elevated blood glucose levels.

Metagenomics The study of the genetics of populations of uncultured microbes.

Microbiome Microbial communities and their host–environmental interactions, in this case, the intestinal tract.

Necropsy- (Necro = death; -opsy = to look) The postmortem (after death) examination of tissues from animal species, analogous to 'autopsy' (auto = self; -opsy = to look) in humans.

Nesidioblastosis (Nesidio = islet; blasto = germ or bud; -osis = condition) A rare type of pancreatic tumor that has proliferation of both ductal and endocrine components.

Abbreviations

DLA	Dog leukocyte antigen
DM	Diabetes mellitus
EPI	Exocrine pancreatic insufficiency
FCoV	Feline coronavirus
MEED	Multisystemic eosinophilic epitheliotropic disease of horses
MHC	Major histocompatibility complex
PAA	Pancreatic acinar atrophy

Introduction

The pancreas is an abdominal tissue that is an essential component of two organ systems, the digestive and endocrine systems. Originally identified by an ancient Egyptian anatomist–surgeon, Herophilus, born in 336 BC, it was later named descriptively 'all-flesh' when written in Greek.

There is little variation in the arrangement of the exocrine pancreas among most mammals, but differences in body structure and metabolism among other members of the animal kingdom are reflected both anatomically and functionally. Among mammals, including human beings, most physiological mechanisms are believed to be homologous. There are, however, important differences in certain diseases, notably pancreatic cancer.

As a component of the digestive system, the pancreas functions as an exocrine gland, secreting digestive enzymes to support release of energy from ingested foods, peptides that modulate the microbiome, and anionic fluids to buffer the pH of the duodenum. As in humans, inflammation of the pancreas has life-threatening or life-ending consequences and is a relatively common condition in carnivores. Neoplasia of the exocrine pancreas is an important disease in dogs and cats but is relatively unknown in horses and most livestock.

The pancreas also has a central, critical role in endocrinologic regulation of multiple metabolic pathways. Control of glucose homeostasis is a central role of the islets of Langerhans, aggregates of endocrine cells that secrete insulin, glucagon, and other hormones into the bloodstream. As in human beings, loss of insulin production or cellular resistance to its actions results in elevated systemic levels of glucose, which manifest as diabetes mellitus (DM). Animals with diabetes do not, however, exactly mimic the disease in humans because of differences in underlying physiology or anatomy. Neurohormonal regulation of the secretory functions of both endocrine and exocrine components of the pancreas involves many different receptors and signaling pathways, which are becoming better characterized during health and disease.

While advancing, our knowledge of the relationships between the pancreas, intestinal tract, and gut microbiome is incomplete. With recent advances in molecular techniques able to query host cell activities and provide metagenomic data regarding metabolism and growth of uncultured intestinal microbes, refining details regarding control of pancreatic secretion and factors that induce inflammation and neoplasia can be expected in the coming years.

Although the pancreas has a central role in survival, it is somewhat an enigma, often relegated to a short section at the end of articles on the gastrointestinal system or liver. There is still much to be learned about this organ, especially in veterinary species. Much of the available information regarding pancreatic function and pathogenesis is derived from investigations of human disease or the use of animals as models for human diseases.

Normal Structure and Function of the Pancreas in Animals

Anatomy

The human pancreas is a retroperitoneal organ with head, neck, body, and tail, while in many companion animals (dogs and cats) and ruminants, the pancreas is a bilobed, V-shaped organ, supported by the mesoduodenum. In dogs and cats, there are usually two pancreatic ducts, one opening at or near the bile duct and a larger duct opening more distally into the duodenum, and several pancreaticoduodenal lymph nodes that are often inconspicuous in health. The horse has a triangular pancreas that is partially retroperitoneal. A thin band of pancreatic tissue, termed the 'portal ring,' wraps around the portal vein in some species (Figure 1).

Among wild or exotic mammals, birds, fish, and reptiles, there is a wide variety of anatomical arrangements, even among relatively closely related species. In the sea otter, for example, the pancreatic parenchyma is distributed in the mesoduodenal adipose tissue while the North American river otter has a distinct bilobed organ. The octopus has a single organ for pancreatic and hepatic functions, the 'hepatopancreas,' from which secretions flow into the pyloric cecum, an appendage of the stomach.

Pancreatic Development

The pancreas develops from the fusion of two endodermal diverticula of the embryonic gut in the region of the duodenum. The two diverticula eventually give rise to the individual lobes of the pancreas. The development of a ductular system is the result of coordinated interplay between the endodermal cells and the local mesenchymal elements. Endocrine components of the pancreas, cells composing the islets of Langerhans and endocrine cells scattered individually between and within acini, are also endodermal in origin. Cell populations that serve as progenitors within the mature pancreas (mesenchymal
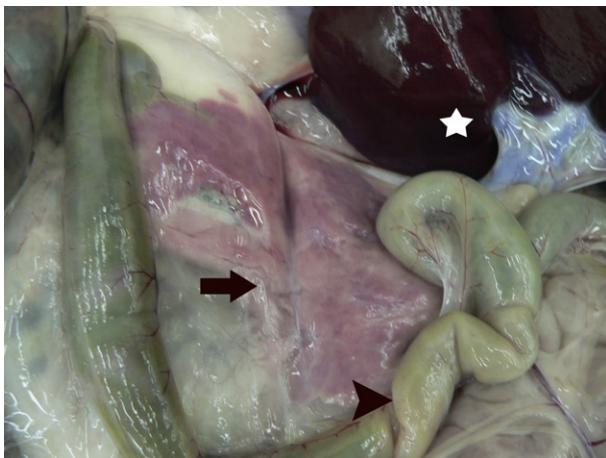

Figure 1   Postmortem image of the grossly normal right lobe of the pancreas (arrow) of a 4-month-old female lamb. The lobe of pancreatic tissue is present in the mesoduodenum. Descending duodenum, arrowhead; caudate lobe of the liver, star.

stem cells) are being defined. The presence of acinar and ductular structures typical of exocrine pancreas within islet cell tumors is likely the manifestation of maturation of progenitor cells along different pathways of differentiation. Understanding the histogenesis and differentiation of islet cells from mesenchymal stem cell populations has developed new importance in recent years as minimal success is met by efforts to transplant insulin-producing beta cells to cure DM. Dogs have been used to study plasticity of pancreatic cell populations and respond to an islet neogenesis-associated protein, an initiator of islet development.

The product of the pancreatic and duodenal homeobox-1 gene is transcription factor that has critical roles in the development of both exocrine and endocrine cells and is expressed by cells of both functional units. With maturation, high levels of expression are limited to endocrine populations producing insulin and somatostatin, while exocrine acinar and ductal cells express low levels of this gene product. The canine homologue has recently been determined to reflect high levels of sequence identity and gene structure, pattern of gastrointestinal and pancreatic expression, and ability to induce insulin biosynthesis with orthologs from other species.

Developmental anomalies of the pancreas that are severe are usually not compatible with life, with animals dying in the neonatal period. Because of a low level of postmortem examinations of neonatal companion and production animals, the incidence of developmental anomalies may be underestimated. Minor developmental anomalies of the pancreas are often clinically silent, due to the large reserve capacity of this organ. Minor anomalies are often identified as incidental findings during examination of tissues for other reasons.

Exocrine Function of the Pancreas

The exocrine portion of the pancreas is a compound tubuloalveolar gland, with acinar cells that produce digestive enzymes and ducts and ductules that convey secretory products to the duodenum. The ductular epithelium also has intrinsic metabolic functions critical to the proper functioning of the digestive system. Acini are spherical to elongated and are connected by stemlike ductal system that are supported by increasing amounts of connective tissue as intralobular ducts come together to form interlobular ducts. The parenchyma is covered by a thin peritoneum and is not surrounded by a distinct capsule. Lobules are separated by thin connective tissue septa and are relatively loosely arranged.

Acinar cells

Acinar cells are pyramidal, are oriented radially around a tiny, central lumen, and have intracytoplasmic, membrane-bound zymogen granules in the apical region. The more basophilic perinuclear region, containing the rough endoplasmic reticulum, gives the acinar cell a two-toned, apical–basal polarized appearance. Catalytically inactive precursor proteins (trypsinogen, chymotrypsin, procarboxypeptidase, proelastase, and kallikreinogen) are synthesized and stored in the zymogen granules, ready for release by granule fusion with the apical membrane when cells are stimulated by cholecystokinin and acetylcholine. Under normal physiological conditions, precursor enzymes are activated once they reach the lumen of the

duodenum, through the sequential activation of trypsinogen to trypsin, followed by trypsin-mediated cleavage of other pro-enzymes (Figures 2 and 3).

The cell volume composed of zymogen granules is highly variable and dependent, in part, on the secretion state of the pancreas, which is related to the physiological need for digestive enzymes. Often, acinar cells within a lobule or group of acini will have similar volume of zymogen granules, which may be different from adjacent lobules, so there may be some level of regional regulation of secretion. During fasting or starvation, autophagic removal of cytoplasmic proteins and decreased
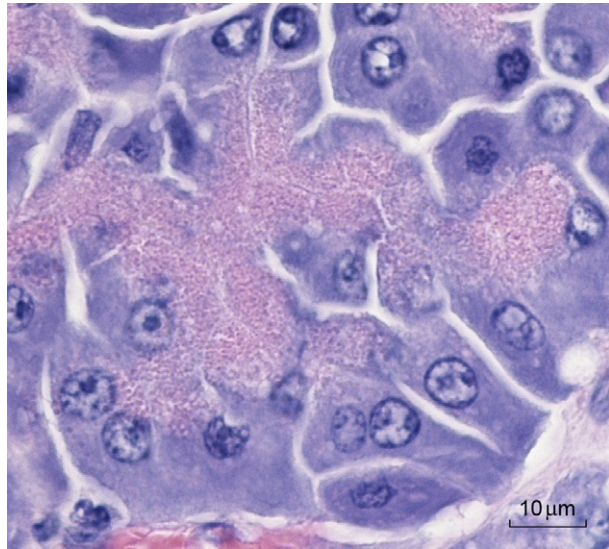

Figure 2 Exocrine cells arranged in acinar groups with a narrow-gauge central duct system that drains proenzyme-rich secretory fluid, delivering it to the ductules. Zymogen granules release their contents by fusion with the apical membrane of the acinar cell. Tissue from an adult, male, Labrador Retriever dog.
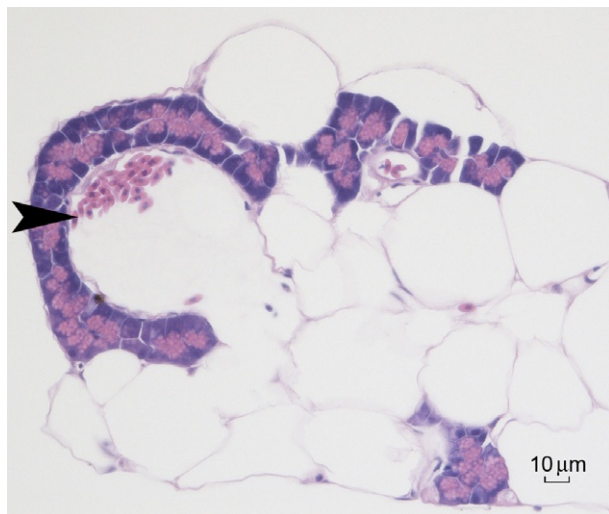

Figure 3 In the fat head minnow fish and other teleosts, acinar groups are distributed throughout the mesentery. Erythrocytes of fish are nucleated (arrowhead).

production of zymogens reduce the size of the acinar cell. Other features of nutritional exocrine atrophy include loss of apical–basal polarity and vacuolation of the cytoplasm. In contrast, high levels of dietary carbohydrate and protein will result in hypertrophy and hyperplasia of the acinar cells. In some animal species, there is seasonal variation of pancreatic morphology. For example, in free-living geckos (Gekkonidae), there is a reduction of acinar cell numbers and therefore exocrine volume during the dry season, when food supplies are scarce.

Ductal system

Pancreatic ducts are lined by columnar cells with luminal microvilli and glycocalyx and small apical cytoplasmic mucin droplets. In large ducts, many epithelial cells also have cilia, which function to aid the downstream movement of exocrine secretions (Figures 4 and 5).
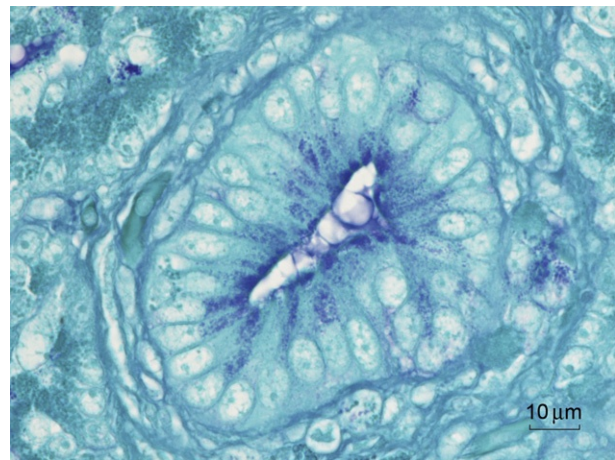

Figure 4 Ductules are lined by columnar cells with apically located, fine intracytoplasmic vacuoles that contain mucins. Periodic acid-Schiff stain.
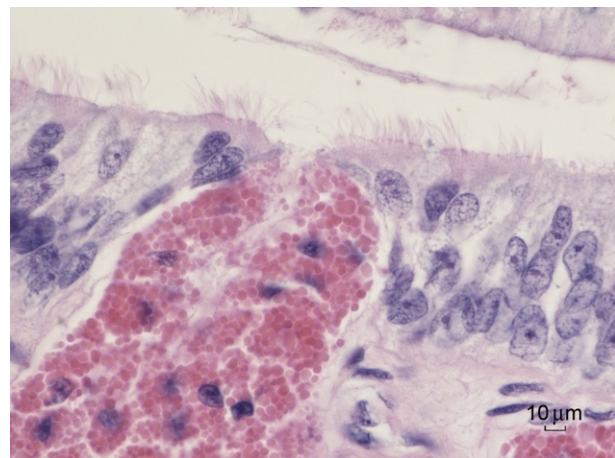

Figure 5 Elongated acini secrete directly into large ducts lined by ciliated, columnar epithelial cells in this pancreas from an adult turtle. Transportation of acinar secretions, including some intact zymogen granules, appears to be facilitated by surface cilia in this species.

Metabolic functions of ductal epithelial cells also are critical to the exocrine function of the pancreas. In addition to serving as a conduit for the transfer of acinar secretory products to the lumen of the duodenum and acting as a barrier between pancreatic parenchyma and its enzyme-rich secretions, the epithelial cells lining the ducts secrete abundant fluid containing bicarbonate and chloride ions. In human beings, epithelial cells lining the ducts may undergo a series of progressively malignant changes that may result in pancreatic ductal adenocarcinoma. Secretion of bicarbonate ions by ductal epithelial cells, giving secretions an alkaline pH (pH $\sim$8), is critical for homeostatic control of the gut microbiome, because this fluid buffers the acidity of the chyme flowing from the stomach into the duodenum.

Immortalized cell lines derived from pancreatic ducts from various animal species, including dogs, cattle, and mice, have been developed as a resource for the study of ductal physiology and carcinogenesis. Important differences in the physiology of pancreatic ductal epithelium between human and veterinary species (which may be important in the selection of model species for human disease) include the absence of a spontaneous cystic fibrosis-like disease among animals and the ductal epithelium as a frequent site of carcinogenesis in humans, but only rarely in veterinary species.

Endocrine Function of the Pancreas

The endocrine function of the pancreas is realized through the hormonal secretions of endodermally derived cells arranged in groups (islets of Langerhans) or scattered individually or in small numbers between the exocrine tissues. Hormones secreted by these cells have critical roles in homeostasis and control metabolism of dietary carbohydrates, lipids, and proteins.

A more complete description of the endocrine physiology of the pancreas is presented elsewhere in this encyclopedia. Briefly, several functionally different populations of endocrine cells in the islet produce and secrete hormones directly into the capillaries that course through the islet. The alpha, beta, delta, gamma (PP), and epsilon cells produce glucagon, insulin and amylin (islet amyloid polypeptide), somatostatin, pancreatic polypeptide, and ghrelin, respectively. Insulin secretion from the islets of Langerhans promotes glucose absorption, lowering blood glucose levels, whereas glucagon has an opposite effect, resulting in elevation of blood glucose levels. Amylin functions to regulate gastric emptying, thus affecting the availability of gastric contents for digestion in the small intestine and affecting the glycemic response. Ghrelin, secreted by epsilon cells of the islet and in the mucosa of the gastric fundus, plays a significant role in the control of appetite, thereby affecting availability of dietary carbohydrate. In the pancreas, pancreatic polypeptide functions to regulate the secretions of pancreatic cells in both endocrine and exocrine compartments. Somatostatin, produced by delta cells and other locations in the digestive system, regulates the release of a variety of hormones, both within the islets and in other organs. Blood flow through the islet and exocrine portions of the pancreas is arranged to sequentially distribute hormones to different environmental niches to coordinate appropriate hormonal control of digestion and metabolism. Immunostaining is used to identify the different populations of endocrine cells (Figure 6).

Small numbers of endocrine cells reside in extrainsular sites, scattered in groups of one to three cells in the thin connective stroma between acini. Immunostaining sections of canine pancreas reveals small numbers of insulin-producing cells in acini. There is the potential for much plasticity among cells in the pancreas, even among highly differentiate populations, with *in vitro* acinar-to-beta-cell transdifferentiation reported, so it may be that this acinar population of extrainsular endocrine cells is derived from acinar epithelial cells.

There is nonhomogenous distribution of the islets of Langerhans within the pancreas and there are differences in distribution of cells within the islets, with different patterns among species. Patterns of distribution of cells and islets match the unique metabolic needs of different species of animals. For example, alpha and beta cells of lizards and snakes alternate in alignment along vascular spaces, instead of the alpha cells surrounding beta-cell architectural islet arrangement as in many other species. The endocrine cells may also be distributed within the spleen of some snakes. The water monitor (*Varanus* spp.) and some lower snakes have a juxtasplenic body that is a large collection of endocrine cells, effectively a large islet, attached to one lobe of the trilobed pancreas. In animals that rapidly ingest carbohydrate-rich meals that generate large amounts of glucose, such as fruit bats, an expanded beta-cell population appears to provide a timely and sufficient insulin response to maintain glucose homeostasis (Figures 7 and 8).

Pancreatic Blood Supply and Innervation

Arterial supply is usually from the celiac artery or a subsidiary, venous drainage is to the portal veins, and innervation is from the celiac and mesenteric plexuses. Afferent blood flows first through small arterioles that penetrate the islets and then serves adjacent acinar glands, effectively integrating the delivery of hormones to the populations of endocrine cells of the islet and to the exocrine cells (Figure 9).

The extrinsic innervation of the pancreas converges on a plexus of intrinsic parasympathetic (cholinergic) pancreatic ganglia embedded in the pancreatic parenchyma that serve to control pulsatile secretion of insulin. Intrapancreatic ganglia are frequently observed microscopically in pancreatic sections from dogs and cats.

In felines, Pacinian corpuscles are frequently encountered embedded in the pancreatic parenchyma and mesenteric stroma. Pacinian corpuscles may be visualized grossly as 1–2 mm diameter, clear nodules that are usually located near the margin of lobules. These viscoelastic mechanoreceptors are well-demarcated, multilamellar structures surrounding a central afferent nonmyelinated nerve ending that detect changes in pressure and vibrations (Figures 10 and 11).

Incidental Findings and Nonlesions

Pancreatolithiasis

In adult cattle, the pancreatic duct may incidentally contain calcium-rich concretions. The presence of pancreatic calculi in cattle does not appear to be associated with pancreatic inflammation. Accumulations of inspissated secretory material, often
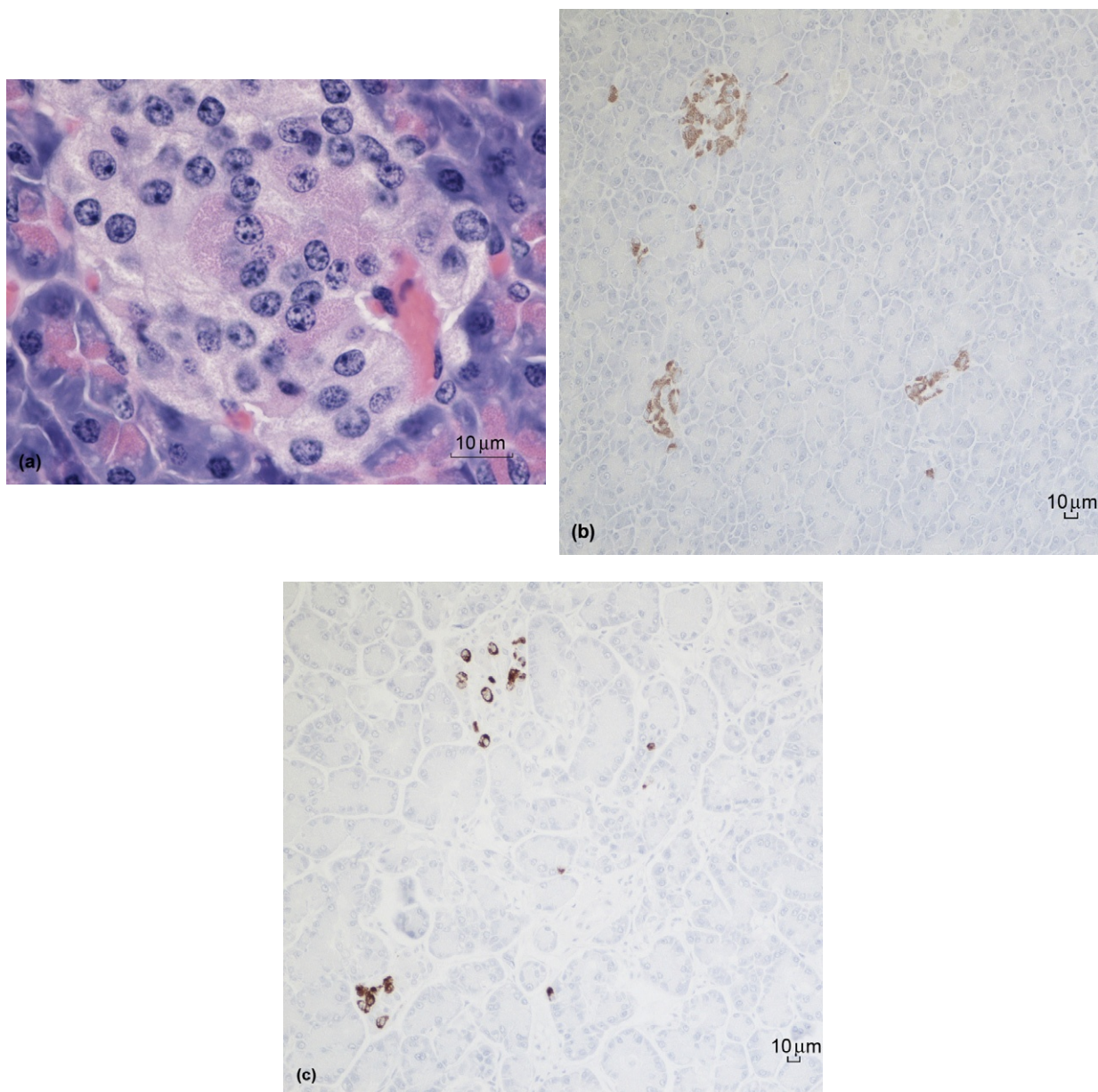
Figure 6 Endocrine cells are located in distinct groups (islets of Langerhans (a)) and scattered in smaller numbers between acini (extrainsular endocrine cells). Immunohistochemical staining with antibodies directed to insulin (b) and glucagon (c) highlights individual populations that are producing hormones. Diaminobenzidine chromogen and hematoxylin counterstain (b), (c).

admixed with debris of inflammatory cells, are, however, a feature of damage to ductal elements in chronic pancreatitis in many other species.

Pancreatic lipomatosis

Adipose infiltration within and between pancreatic lobules, in the absence of clinical signs or histological features of DM, is a common finding in obese and aged animals and has long been considered an incidental finding as no overt clinical signs have been associated with this condition. As a better understanding of the relationships between adiposity and systemic disease (such as DM and low-grade systemic inflammation) is developed, the view of this condition as incidental may change,

particularly in species prone to type 2 DM (discussed in the succeeding text in this article). Increased amounts of lipid are stored as intracellular triglyceride in cells usually located at the periphery of lobules or in septa, suggesting storage in mesenchymal cells of the septal stroma. Apparent expansion of the volume of mesenteric adipose tissue also occurs in exocrine pancreatic insufficiency (EPI) (discussed later in this article), concurrent with loss of acinar volume (Figure 12).

Heterotopic pancreatic tissue (pancreatic exocrine choristoma)

Groups of pancreatic cells in nontraditional locations, including the wall of the stomach, intestine, or gallbladder,
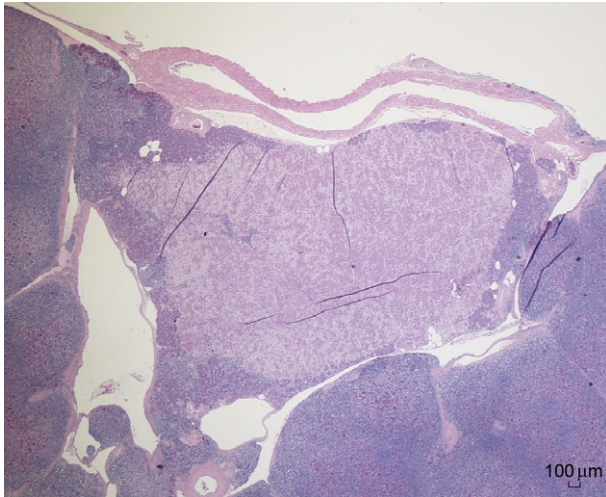
Figure 7   An extreme example of the variety of anatomical organization of endocrine and exocrine components; endocrine cells are centralized in the juxtasplenic body of this Malaysian water monitor (*Varanus salvator*). A thin and discontinuous rim of exocrine tissue (arrow) surrounds the sheets of pale eosinophilic endocrine cells. This region is attached to one of the three lobes of pancreatic tissue in this species. Case material courtesy of Dr. Amanda Fales-Williams, Iowa State University.
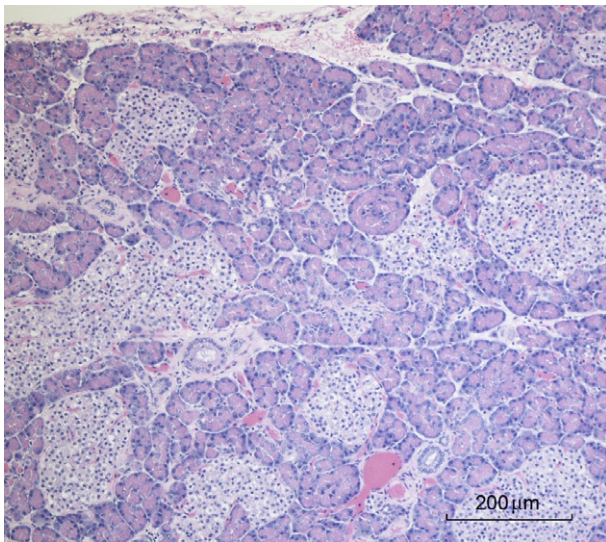

Figure 8   The distribution and amount of endocrine tissue within the pancreas vary among species. In the pancreas of an Egyptian fruit bat, whose diet contains abundant, readily digestible carbohydrate, the islets of Langerhans are large and comprise a high percentage of the pancreatic parenchyma. Case material courtesy of Dr. Michael Yaeger, Iowa State University.

Figure 9   Afferent blood to the pancreatic parenchyma flows first through a capillary in the center of the islets of Langerhans (arrow), then peripherally around the islet, and eventually to the nearby acini. This glomeruloid pattern of blood flow allows hormones secreted directly into the blood by endocrine cells in the islet to rapidly coordinate local endocrine and exocrine activities.

Figure 10   Intrapancreatic ganglion. Innervation of the pancreas is via the celiac and mesenteric ganglia, with intrinsic ganglia such as this one that provides local regulation of insulin secretion. Pancreas from an 8-year-old, male, Golden Retriever dog.

mesentery, or in the liver or spleen, are reported occasionally in animals. Animal species in which heterotopic pancreatic tissue have been reported include the dog, cat, horse, cynomolgus macaque, and rat. Ectopic pancreatic tissue usually consists of well-differentiated acini with ducts, sometimes with interspersed islets. The presence of aberrantly located pancreatic parenchyma is probably due to heteroplastic differentiation of embryonic endoderm or, in the case of pancreatic tissue in the wall of the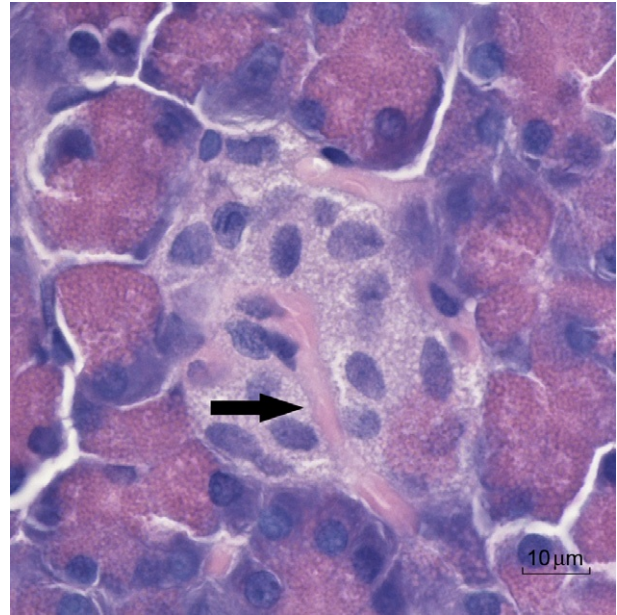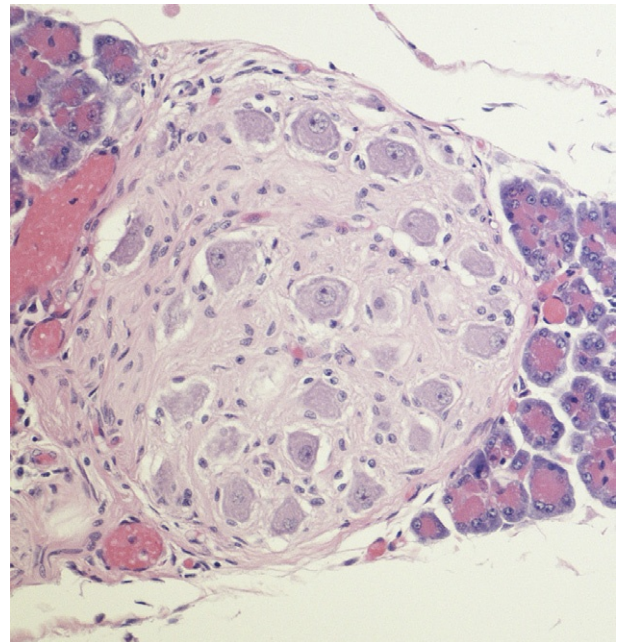 duodenum, incomplete migration of primordial endodermal cells followed by differentiation to pancreatic cells. Heterotopic pancreatic tissue is theoretically susceptible to a range of pathologies, but reports of such are rare (**Figure 13**).
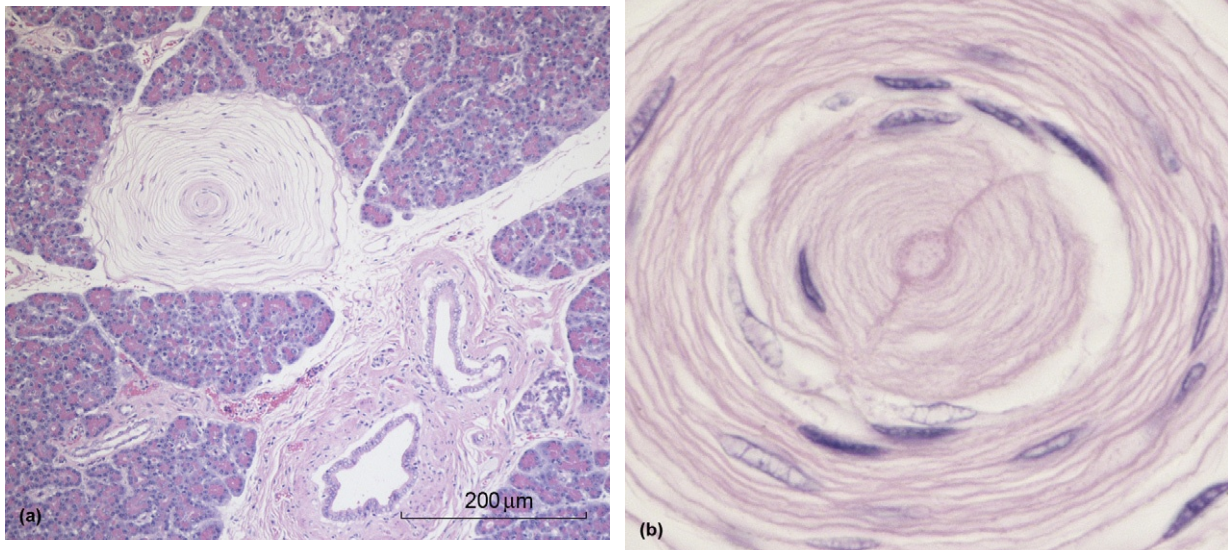
Figure 11 Pacinian corpuscle. Pacinian (lamellar) corpuscles are frequently observed embedded within the feline pancreas (a), less commonly in other species. These structures serve as mechanoreceptors, sensing vibration and pressure. Centrally within the multilaminar system of capsules is a single nerve ending (b).
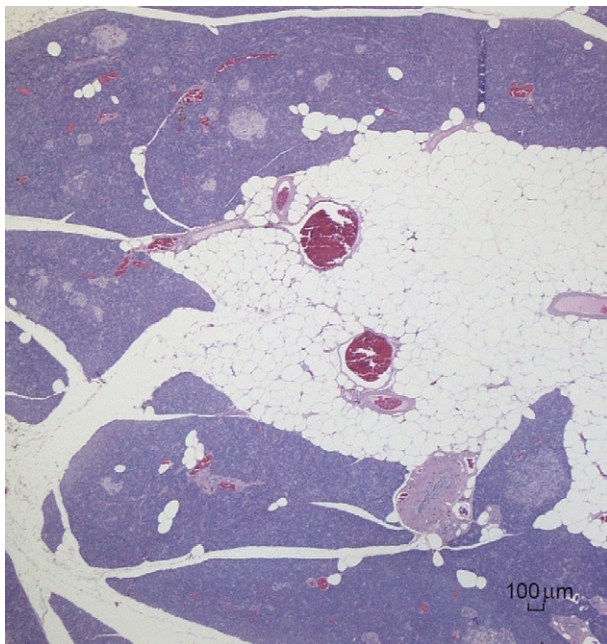

Figure 12 Abundant adipose tissue is present as sheets between pancreatic lobules and as small groups of cells within lobules. Also in this image, many islets are expanded by eosinophilic material (consistent with amyloid), but other clinical or histological features of diabetes mellitus (DM) were absent. Tissue from a 10-year-old, domestic short-haired cat that died of cerebral lymphoma.

Figure 13 Heterotopic pancreatic tissue in the wall of the duodenum in an adult, mixed-breed dog with acute pancreatitis. A well-demarcated island of exocrine tissue is present between muscular tunics (arrow) and is undergoing early degeneration, similar to the normally located lobules. Suppurative inflammation and fat necrosis also are present in the adjacent mesentery (arrowhead). Duodenal mucosa, star.

Intrapancreatic heterotopic splenic parenchyma (intrapancreatic splenic choristoma)

Rarely, the pancreatic parenchyma is the site of nodules of functional splenic tissue in rabbits, nonhuman primates, cats, and dogs. Intrapancreatic accessory spleens are small, single or multiple nodules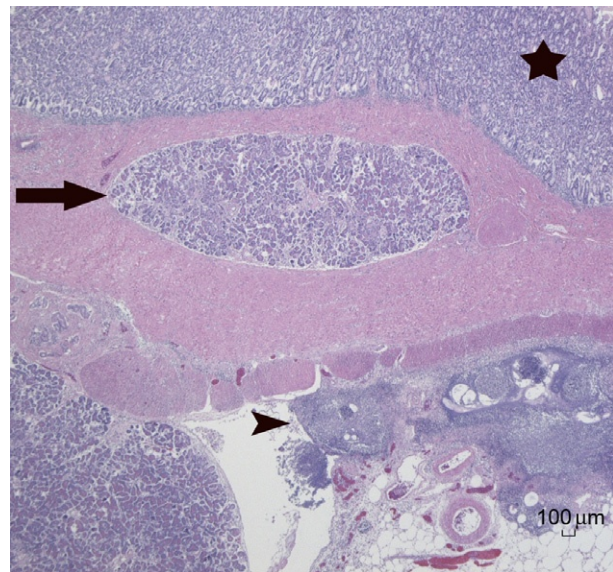, are usually considered to be congenital, and are incidental findings. Microscopic features are consistent with normal splenic tissue with red and white pulp contained within a partial or complete connective tissue capsule. Differential diagnoses include primary pancreatic neoplasia or metastatic neoplasia (especially when concurrent with splenic hemangiosarcoma, a relatively common malignancy in dogs) (**Figure 14**).
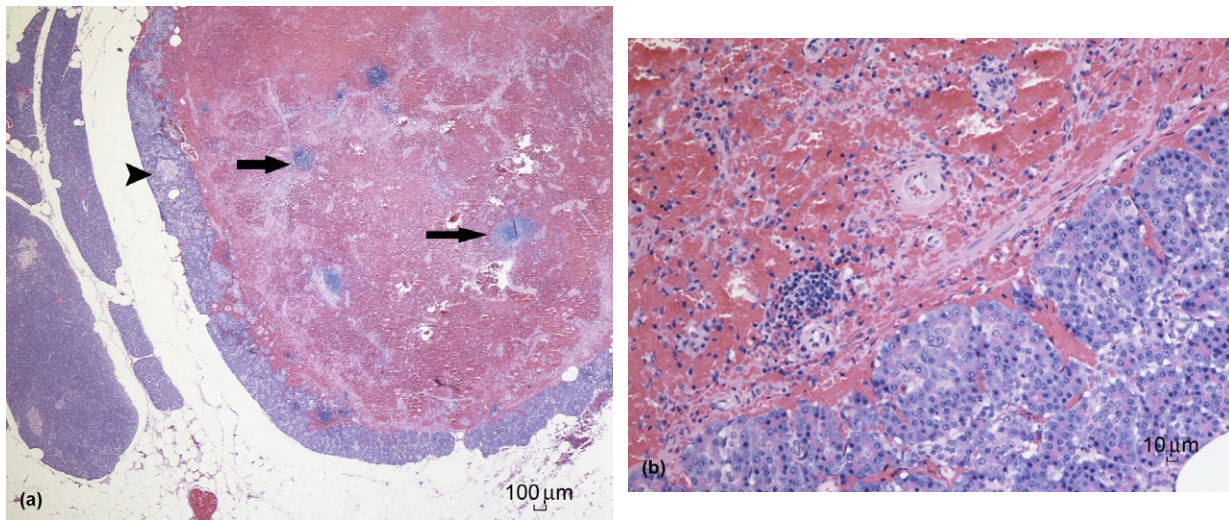
Figure 14   Heterotopic spleen within the pancreas of an adult, domestic short-haired cat (a). This lesion was an incidental finding at necropsy. Note the red pulp with abundant blood and scattered, thin, fibromuscular trabeculae and white pulp consisting of periarteriolar lymphocytic sheaths (arrows) within a lobule of pancreatic parenchyma (b). An islet (arrowhead) is visible in (a).

Considerations for Microscopic Evaluation of Pancreatic Tissues

Histological examination of biopsy or postmortem (necropsy) samples is required for the definitive diagnosis of many pancreatic diseases. During collection of pancreatic tissue for microscopic evaluation, tissues should be handled gently and, in the case of postmortem samples, collection should be performed as soon after death as practically possible, to reduce artifactual changes.

Increasingly common in recent years since laparoscopic methods for abdominal exploration have become commonplace, pancreatic biopsy specimens from dogs and cats are seen more frequently among surgical biopsy samples. These samples are often tiny and may not be representative of pancreatic lesions, but as exploratory laparotomy is contraindicated in many severely ill patients, these samples sometimes provide otherwise unobtainable information. Laparoscopic punch biopsy does not appear to alter the clinical course of veterinary patients that undergo this procedure or to elevate serum enzyme levels, but biopsy sites in patients that later undergo postmortem examination are noted to be foci of variably intense hemorrhage and inflammation (Figure 15).

The pancreas is notoriously susceptible to postmortem autolysis, and light microscopic interpretation of pancreatic sections must take into consideration this possibility. Importantly, differentiation of post- and antemortem autolytic changes is critical to the diagnosis of pancreatic inflammation, which has an autolytic component. Early autolytic changes include sloughing of the ductal epithelium and disruption of acinar architecture, followed by loss of cytoplasmic definition, with apparent lysis of zymogen granules, and condensation of nuclear chromatin. Karyolysis and cytolysis soon follow. Due to the relationship between the pancreatic duct system and intestinal tract, bacteria are sometimes present in autolytic regions, usually in highest concentrations near vessels and ducts, suggesting retrograde movement from the portal tract or pancreatic ducts (Figure 16).
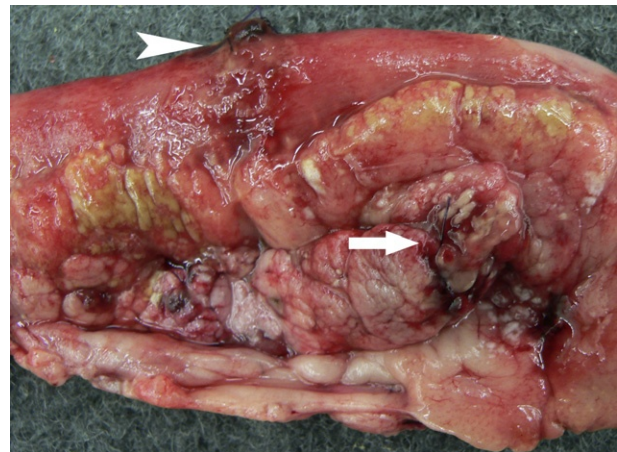

Figure 15   Pancreatic (arrow) and intestinal (arrowhead) biopsy was performed during exploratory laparotomy in an 8-year-old, male, Dachshund dog with a history of melena, anorexia, and vomiting. Microscopic features of acute necrotizing pancreatitis and enteritis with early biopsy site dehiscence were present in tissues examined later at necropsy.

Diseases of the Exocrine Pancreas

Pancreatic Acinar Atrophy and Exocrine Pancreatic Insufficiency

Exocrine pancreatic insufficiency (EPI), a clinical maldigestion syndrome of dogs characterized by weight loss, diarrhea, steatorrhea, is caused by failure of the pancreas to synthesize and secrete adequate amounts of digestive enzymes. In dogs, EPI appears to be caused most frequently by the atrophy and loss of enzyme-producing acinar cells, termed pancreatic acinar atrophy (PAA), as the result of an autoimmune mechanism directed to acinar epithelial cells. Clinical diagnosis is based on characteristic clinical signs of weight loss in the face of a voracious appetite, abundant, gray, malodorous feces, and low levels of serum trypsin-like immunoreactivity (TLI) or fecal hydrolase (Figure 17).
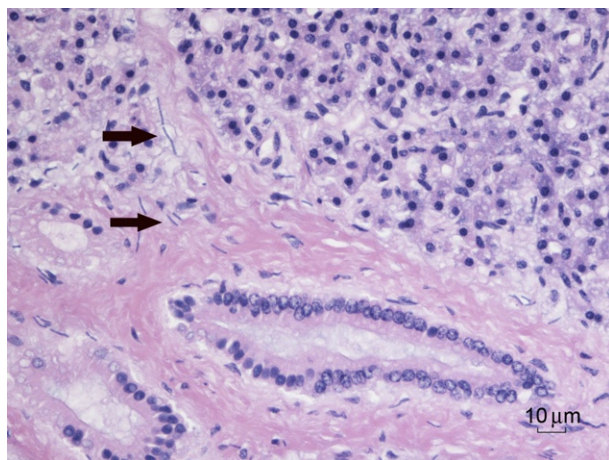
Figure 16 Autolytic pancreatic tissue from an adult horse that died of colic (intestinal rupture with endotoxic shock). Note the disruption of acinar architecture, loss of zymogen granules, and presence of rod-shaped bacteria without a neutrophilic response.
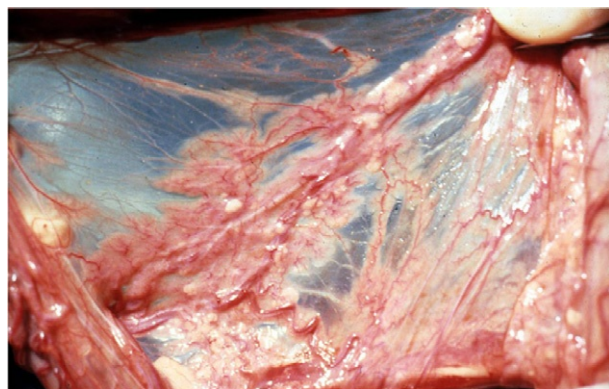

Figure 17 The duodenal limb of the pancreas of a dog with pancreatic acinar atrophy. Reproduced from Westermarck et al., 2012. Top. Companion Anim. Med. 27 (3), 96–103.

EPI affects dogs of many breeds, with distinctly enhanced risk of occurrence in the German shepherd, rough-coated Collie, Chow Chow, and Cavalier King Charles spaniel breeds of dogs. Originally believed to be a simple autosomal recessive trait, recent work examining the canine major histocompatibility complex in affected German shepherd dogs points to a more complex mechanism of inheritance, probably as the result of a combination of genetic and epigenetic/environmental factors. Protective and high-risk haplotypes of dog leukocyte antigen (DLA) have been identified.

This disease is slowly progressive, with underlying pathology for an extended time before overt disease is noticed, because of the large reserve capacity of the pancreas for the secretion of digestive enzymes. Prior to clinical signs, the subclinical phase of pancreatic inflammation is characterized by infiltration of exocrine lobules by T lymphocytes, with fewer plasma cells and macrophages. Individual lymphocytes are present in acini and ductal epithelium or may form lymphoid follicles. Low levels of serum TLI, a pancreas-specific marker, support a diagnosis of exocrine insufficiency.

With continued infiltration of lymphocytes, acinar epithelial cells undergo degeneration and necrosis, which results in loss of the pancreatic parenchyma. Sharply demarcated border zones between affected and minimally affected regions are typical. Electron microscopic changes include dilation of the rough endoplasmic reticulum, mitochondrial swelling, and fusion of zymogen granules within acinar cells. Scattered apoptotic acinar cells and autophagocytic vacuoles also are present. During the subclinical phase, these changes are reflected in reduced serum TLI levels.

Eventually, sufficient parenchyma is lost to result in clinical signs of maldigestion, namely, steatorrhea. In late stages of the disease, the pancreas consists of small numbers of disorganized acini infiltrated by fewer numbers of lymphocytes, with prominent residual islets containing insulin-producing cells, and mature adipocytes that replace lost parenchyma. Fibroplasia is usually scant. In some areas of damaged exocrine parenchyma, regenerative duct-like structures appear to be formed from a progenitor cell population.

Combined Exocrine and Endocrine Pancreatic Atrophy in Juvenile Dogs

Failure or concomitant loss of exocrine and endocrine pancreatic function is reported rarely in young dogs. In one series of greyhound dogs, marked loss of pancreatic parenchyma was characterized by widespread atrophy of lobules with degenerative changes in acinar cells, including apoptosis, loss of zymogen granules, intracytoplasmic vacuolation, and loss of islet cells. In animals available for antemortem evaluation, concurrent exocrine insufficiency and insulin-dependent DM were present. The cause of this syndrome is not currently known. Except for two siblings evaluated, the genetic relationship of affected dogs was not reported. Ductal damage or periductal inflammation was not observed, ruling out the possibility of an ascending etiology. A variably intense infiltrate of lymphocytes and plasma cells was present in some lobules, suggesting the possibility of an immune-mediated mechanism. A similar concurrent loss of exocrine and endocrine elements has been described in a small number of young Beagle dogs.

Secondary Pancreatic Atrophy

Loss of pancreatic parenchyma and the clinical appearance of a small, firm, nodular pancreas, diffusely or regionally, are relatively common among dogs and cats and are usually the sequel of chronic, fibrosing pancreatitis. In contrast to the apparently inherited, primary pancreatic atrophy described earlier, damage to the parenchyma during acute pancreatitis or pancreatic necrosis results in degeneration or loss of acinar structures and is usually followed by proliferation of fibrous tissue. As a physiological mechanism, atrophy of acinar cells without fibrosis also occurs with inappetence or starvation, as described earlier in this article.

Pancreatic Exocrine Nodular Hyperplasia

Hyperplastic exocrine nodules are very common incidental findings in older dogs and cats and occur sporadically in cattle. Multiple hyperplastic nodules are usually interspersed between

normal lobules and consist of slightly raised, discrete, white-tan nodules randomly scattered throughout the organ. Affected lobules are similar in size to adjacent normal lobules and are minimally expansile. Varying degrees of acinar cell hyperplasia are usually present among the multiple hyperplastic nodules in a single patient. Hyperplastic acinar cells have features consistent with their normal counterparts and often have more or fewer zymogen granules than adjacent apparently normal lobules. Hyperplasia of ductular cells is uncommon. The stimulus (or stimuli) for proliferation is not known, but does not appear to be related to regeneration after pancreatic injury, because evidence of prior damage is usually absent or minimal. Additionally, because of the high frequency of spontaneously occurring hyperplastic nodules and the low incidence of pancreatic carcinoma in animals, it is not likely that hyperplastic nodules represent an early stage of carcinogenesis (Figure 18).

Exocrine Pancreatic Adenoma

Benign neoplasia of the exocrine pancreas (pancreatic adenoma) is not commonly reported. As adenomas do not appear to progress to malignancy and therefore have low clinical significance, they are considered an incidental finding. Exocrine adenomas are thinly encapsulated and have an expansile growth pattern, sometimes causing compression and atrophy of adjacent lobules. Cells comprising acinar adenomas resemble normal acinar cells. The molecular events that lead to the formation of exocrine adenomas in domestic animals are not known (Figure 19).

Exocrine Pancreatic Adenocarcinoma

Malignant neoplasms arising from acinar or ductal elements of the pancreas are uncommonly reported among veterinary species, with carnivores (pet dogs and cats) having the highest incidence. Pancreatic adenocarcinoma is rarely reported in horses, cattle, swine, and exotic animals. As with most neoplasms, incidence increases with age.

Adenocarcinomas may be solitary or multiple nodules that efface local pancreatic parenchyma. By the time of diagnosis, pancreatic adenocarcinomas have invaded locally and undergone transcoelomic or vascular/lymphatic metastasis. Similar to ductal adenocarcinomas of humans, invasion and metastasis occur early in canine and feline patients, with destructive invasion locally and regionally and metastasis across the coelomic cavity and to distant organs such as the lung, liver, and other organs. Concurrent inflammation and atrophy of adjacent, nonneoplastic parenchyma and mesenteric steatitis with fat saponification are usually present (Figure 20).

In contrast to this disease in human beings, where infiltrating ductal adenocarcinomas represent the majority of carcinomas, pancreatic carcinomas of carnivores have a range of morphologies that reflect acinar and ductal differentiation, within and between tumors. Carcinomas composed of cells with differentiation reminiscent of zymogen-filled acinar cells are designated acinar cell carcinomas. Other carcinomas have a tubular architectural arrangement of neoplastic cells with formation of lumens in some groups of cells, reflecting duct-like differentiation. Cytological features of malignancy are also variable among neoplastic cells, ranging from mild to marked nuclear atypia, few to many mitoses, and nuclear to cytoplasmic ratios that usually reflect the degree of differentiation. Differences in morphology with regard to acinar or duct-like appearance do not appear to affect prognosis, which is grave. A dense fibrous (desmoplastic) response commonly present surrounding poorly differentiated pancreatic carcinomas may result in a firm texture. There is a subtype of pancreatic cancer in dogs, hyalinizing pancreatic carcinoma (described in the following text in this article), that appears to have a less aggressive clinical course (Figures 21–23).

Exocrine pancreatic cancer may be derived from cells with ductal or acinar differentiation or perhaps from progenitor populations in the pancreas. The histogenesis of exocrine carcinomas in veterinary patients is not defined. Likewise, precursor lesions have not been identified. Molecular defects that cause loss of regulation of differentiation and proliferation of
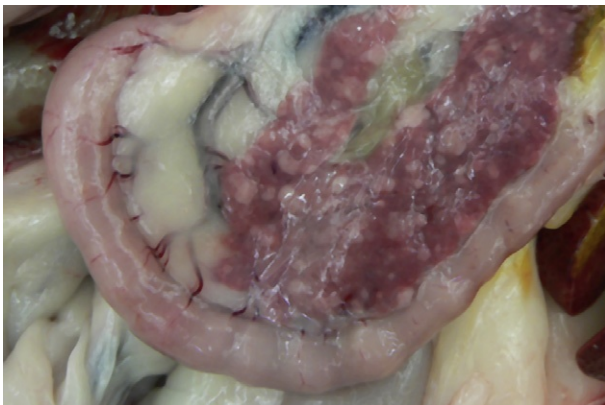

Figure 18 Exocrine nodular hyperplasia. Scattered through the pancreatic parenchyma in this 13-year-old, male-neutered, domestic long-haired cat are multiple, firm, tan-white nodules of exocrine hyperplasia.
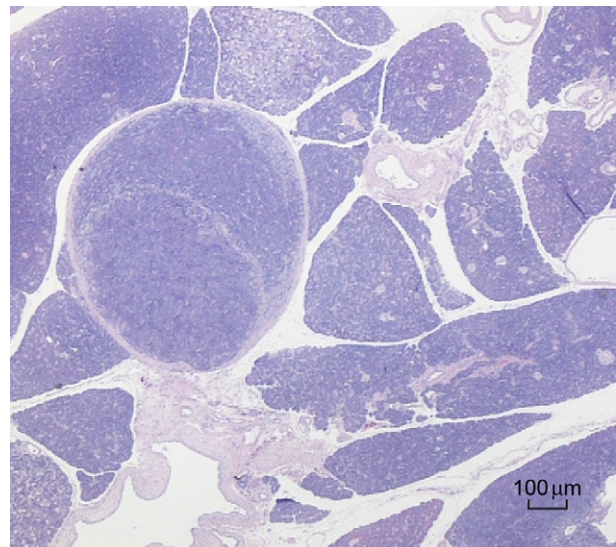

100 µm

Figure 19 Exocrine adenoma. A single, focal, thinly encapsulated pancreatic adenoma is present in the pancreas of a 22-year-old, male-neutered, domestic short-haired cat.
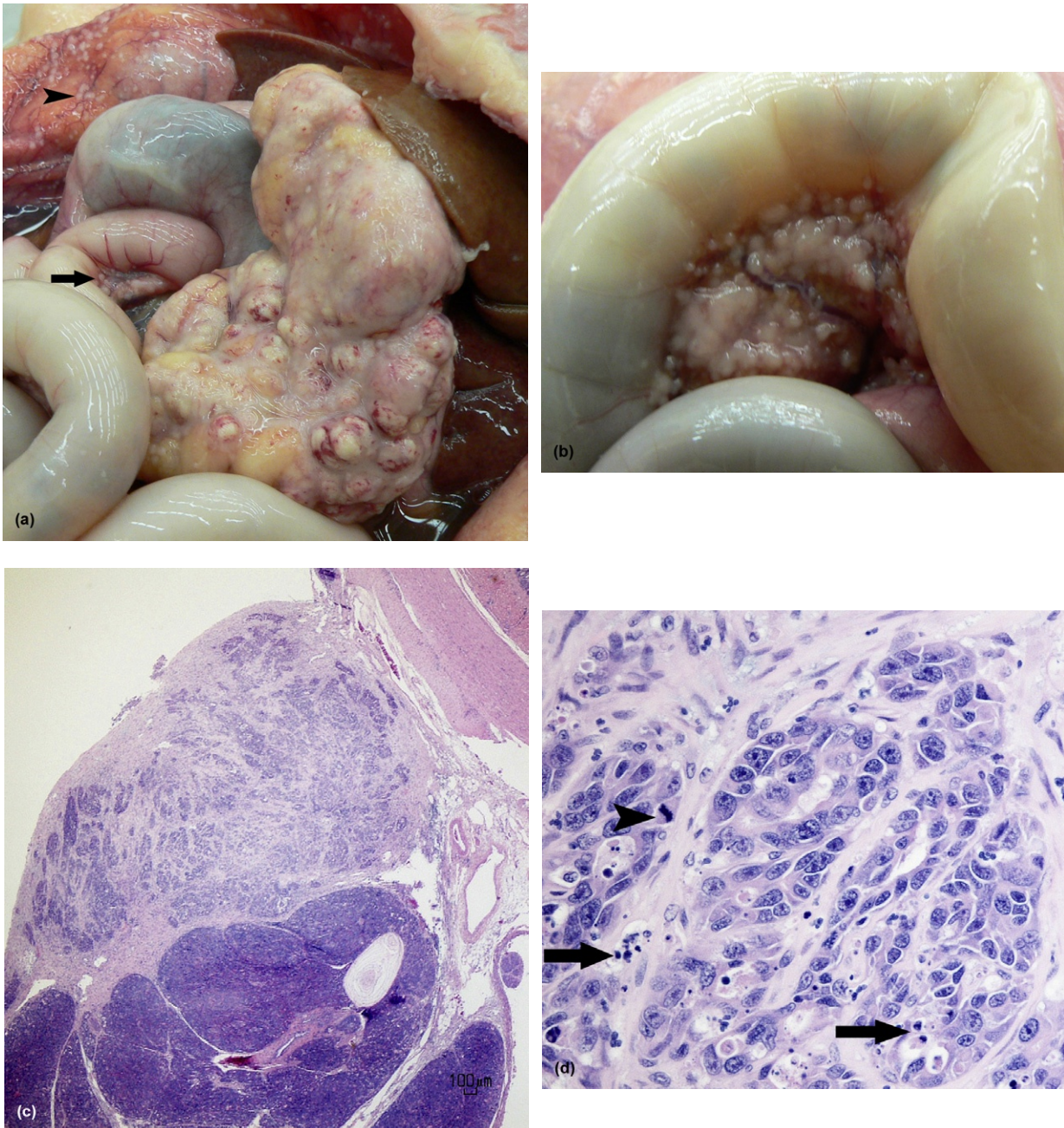
Figure 20 A poorly differentiated, ductular pancreatic carcinoma effaces the architecture of the pancreas and mesoduodenum (a) of a 10-year-old, male-neutered, domestic long-haired cat and has undergone transcoelomic metastasis (carcinomatosis) to the mesentery of the jejunum (arrow) and parietal peritoneum (arrowhead) (a), (b). In a minimally affected region of this pancreas, a nodule of neoplastic cells effaces lobular architecture in the mesoduodenum (c). This neoplasm is composed of groups of proliferating, poorly differentiated polygonal cells forming scattered duct-like structures (d). There is abundant apoptotic debris (arrows) and a mitotic figure (arrowhead) in this image.

precursor cells are not currently known. The disease does not appear to have an inherited (breed-related) cause. A report of an apparent increased risk in the Airedale terrier dog from the 1970s has not been confirmed or refuted. There is scant research in veterinary fields to identify the underlying molecular basis for malignancy. A recent study of canine exocrine pancreatic acinar cell carcinomas demonstrated loss of claudin-4, an integral membrane protein of intercellular tight junctions, from cells comprising acinar cell carcinomas, which may be related to local invasiveness.

Canine hyalinizing pancreatic carcinoma

A rare form of exocrine pancreatic carcinoma with abundant, hyaline extracellular material has recently been reported. Tumors were usually present as a singular mass in the right lobe of the pancreas. Microscopically, groups of neoplastic
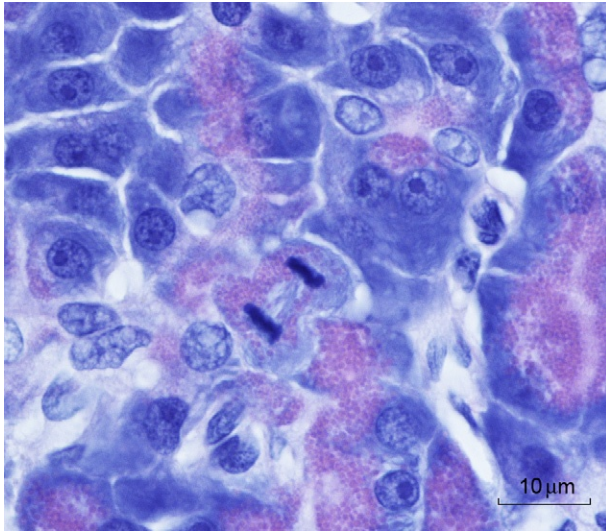
Figure 21 Pancreatic plasticity is demonstrated by this well-differentiated acinar cell undergoing mitosis. This tissue is from a canine patient with pancreatic adenocarcinoma in an adjacent lobule.
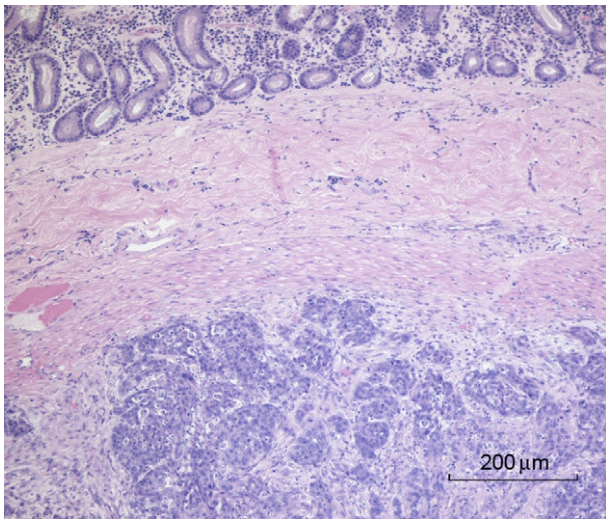

Figure 22 Invading front of an acinar carcinoma. Groups of neoplastic exocrine cells invade the wall of the small intestine of an adult, mixed-breed dog. Groups of neoplastic cells are surrounded by a desmoplastic reaction composed of immature fibrous tissue with inflammatory leukocytes. Also present is a lymphoplasmacytic infiltrate in the lamina propria.

cells with apical zymogen granules are arranged as tubules and acinar structures. Abundant, brightly eosinophilic material of unknown composition fills the lumens of tubules and expands the stroma. The hyaline material is not congophilic and immunonegative for amyloid, immunoglobulin light chains, islet amyloid polypeptide, laminin, or alpha-1-antitrypsin. Features of malignancy, such as absence of a capsule, mild cellular atypia, frequent mitotic figures, and stromal invasion, were present. An extended survival time (>15 months), even in the presence of metastatic disease, was reported in two dogs.
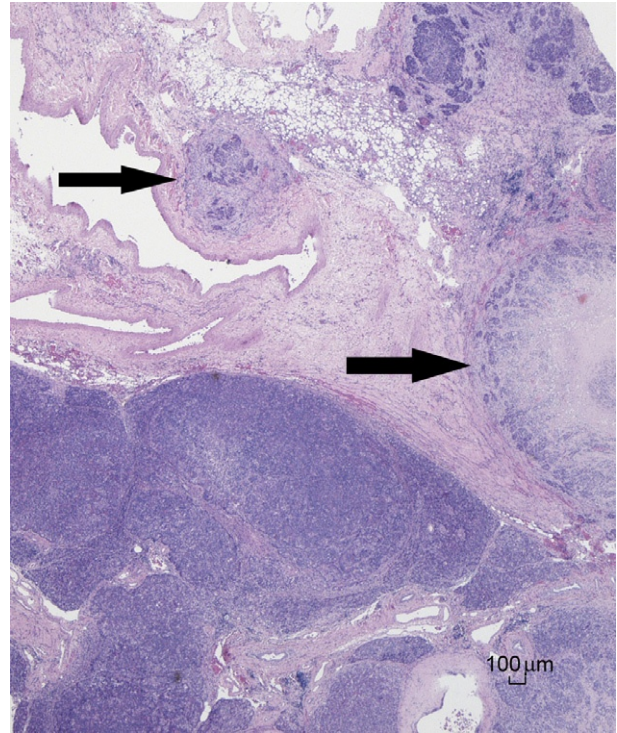

Figure 23 Groups of malignant cells (arrows) have invaded the peripancreatic tissues where an intense desmoplastic reaction has been induced.

The development of paraneoplastic panniculitis appears to be frequent among patients with this neoplasm (**Figure 24**).

Paraneoplastic panniculitis

Inflammation of the subcutaneous adipose tissue has been reported as a comorbidity with pancreatic disease, including neoplasia, in dogs, cats, and human beings. Patients present with multifocal, draining, truncal cutaneous nodules. The underlying lesion is chronic destruction of the subcutaneous adipose tissue, with an intense inflammatory response composed of neutrophils and macrophages. The pathogenesis appears to be related to the release of activated digestive enzymes, that is, lipase, from damaged pancreatic tissues, and speculated mechanisms include systemic release of lipolytic enzymes from neoplastic tissue, perhaps through 'leaky' intratumoral blood vessels. Once in the systemic circulation, circulating enzymes are speculated to damage blood vessels, escape into the surrounding tissues, and cause fat necrosis. Alternatively, or perhaps concurrently, a deficiency of enzyme inhibitors such as alpha-1-antitrypsin or alpha-2-macroglobulin may predispose patients to this rare condition (**Figure 25**).

Nesidioblastosis

Nesidioblastosis is defined as the proliferation of both ductular and islet cells, with hypertrophy of beta cells in islets and the formation of ductuloinsular complexes (closely associated groups of proliferating endocrine cells and small exocrine ducts). In human beings, this condition is associated with hyperinsulinemia and hypoglycemia in the absence of an
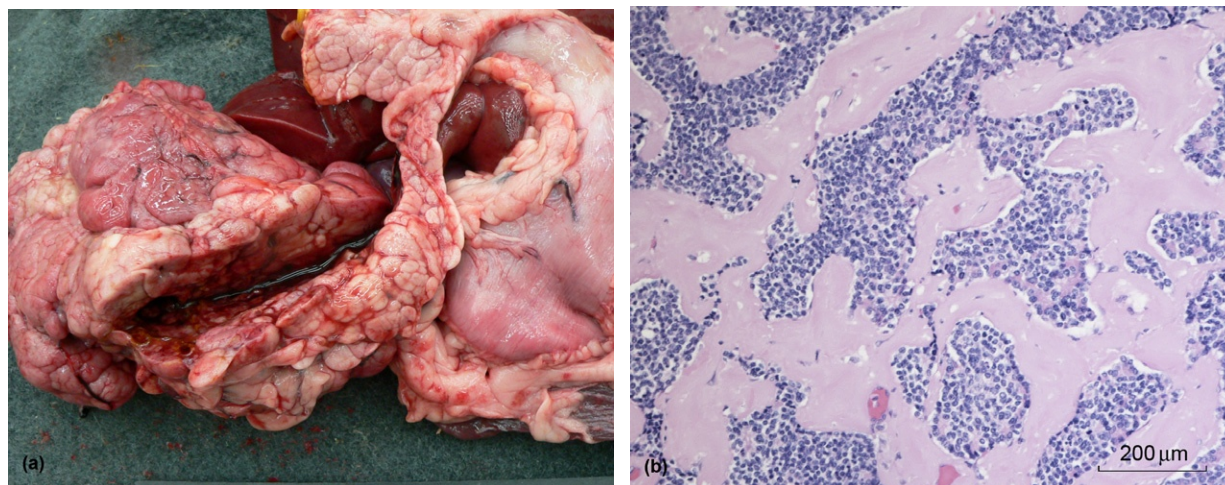
Figure 24 Hyalinizing pancreatic carcinoma in a 6-year-old, female-spayed, Tibetan Terrier dog. The left lobe of the pancreas is effaced by a multinodular, moderately firm, tan mass similar to normal pancreatic parenchyma (a). Metastatic lesions were not found. Microscopically, in multiple regions, there are cords of neoplastic polygonal cells interspersed with abundant, paucicellular hyaline material (b). Scattered acinar- or duct-like structures are present in cords of cells. Gross image and case material courtesy of Dr. Ronald Myers, Iowa State University.
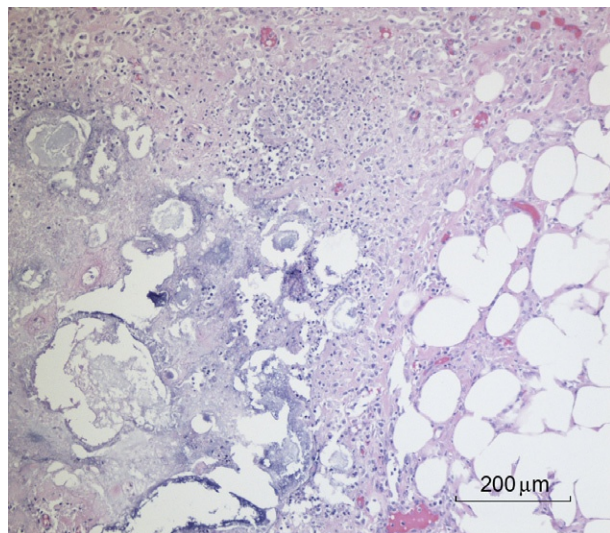

Figure 25 Pancreatic panniculitis. Sterile panniculitis in a 6-year-old, female-spayed, Tibetan Terrier dog that had hyalinizing pancreatic carcinoma as shown in **Figure 24**. Clinically, the dog had a 2-week history of draining, nodular skin lesions and markedly elevated serum lipase. Necrotizing and pyogranulomatous panniculitis with fat saponification and fibrosis are present. Case material courtesy of Dr. Ronald Myers, Iowa State University.

insulinoma. Well-defined groups of irregularly or haphazardly arranged cells are present within exocrine lobules. This condition is reported in the veterinary literature occasionally, but usually without clinical signs associated with hyperinsulinemia. Ductuloinsular complexes typical of nesidioblastosis were recently described in a Simmental calf with arthrogryposis. Proliferating beta cells expressed low levels of insulin. Similar lesions composed of proliferating endocrine and exocrine ductular epithelial cells have been reported in dogs. Twenty nine of three hundred and thirty-two dogs in a cohort of young Beagle dogs were reported to contain this change. The condition was most prominent in young dogs. Hyperglycemia and progressive weight loss have been reported in two squirrel monkeys with immunohistochemical evidence of glucagon production by proliferating endocrine cells (**Figure 26**).

Pancreatitis

Inflammation of the pancreatic parenchyma may occur as a specific entity (usually in the dog) or as a component of a variety of systemic or multifocal diseases or conditions that impact this organ. Pancreatitis may be an acute, temporary condition or, if the inciting stimulus remains or damage is sufficiently severe, may result in permanent loss of exocrine and/or endocrine function. Pathogenic mechanisms of acute and chronic inflammation of the pancreatic exocrine tissues are believed to be similar among mammals, so information derived from studies of human patients is often applied to veterinary patients.

The clinical diagnosis of pancreatic inflammation depends heavily on the evaluation of serum levels of pancreatic enzymes. As new biomarkers of pancreatic injury are identified, retrospective evaluation of the specificity of serum assays, involving correlation of clinical signs, clinicopathologic data, and necropsy finding provide information regarding prognostic value of these tests. Canine pancreas-specific lipase levels are useful in determining clinically the presence of pancreatic inflammation, except for pancreatic infiltration by lymphocytes. TLI, measured independently for each animal species, is a useful test for pancreatic inflammation. Limited information is available for serum enzyme activities, tissue sources, and reference ranges in nondomestic animal species, but reference ranges for various biomarkers of pancreatic pathology are becoming available for exotic animal species.

Acute necrotizing pancreatitis/acute pancreatic necrosis

Acute necrotizing pancreatitis is a condition generally seen in small companion animals (dogs and cats). Recent work has highlighted this condition as previously underdiagnosed in

cats. The cause of acute pancreatitis in dogs is not known, but patients with acute pancreatitis are typically older, obese, female, or female-spayed, miniature breed dogs. Dog breeds at increased risk of developing acute pancreatitis include miniature schnauzer, Yorkshire Terrier, and cocker spaniel dogs, but genetic studies to identify specific mechanisms have not been performed. The Labrador retriever dog appears to have a reduced risk of acute pancreatitis. Other risk factors include ingestion of a high-fat meal, endocrine disease (hyperglucocorticoidism or hypothyroidism), hypercalcemia, uremia, trauma, or treatment
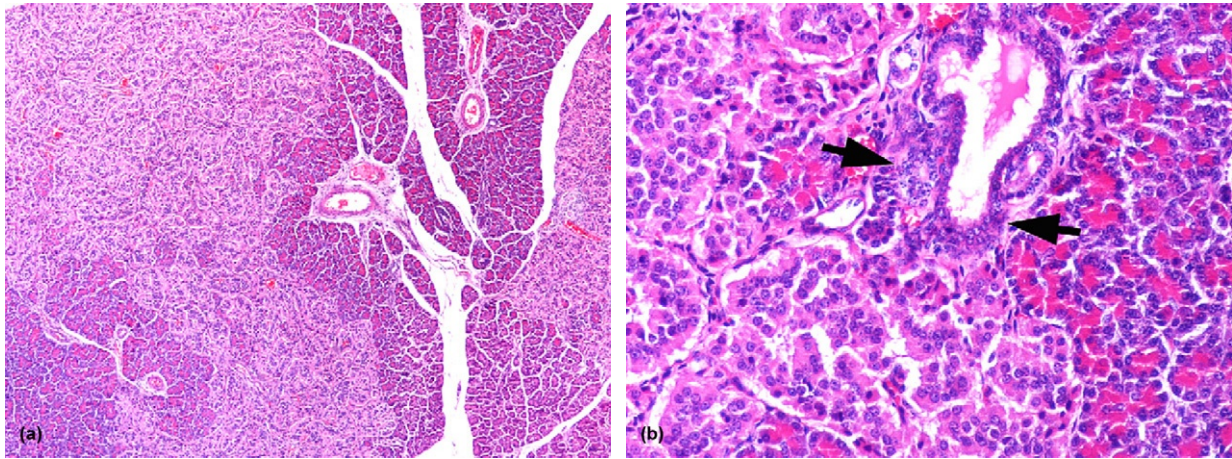

Figure 26   Groups of hyperplastic cuboidal to columnar cells compress acini within lobules of exocrine pancreas (a). Proliferating endocrine cells bud from the ductular epithelium (b). Reproduced from Gacar et al., 2012. J. Comp. Pathol. 147 (4), 491–494.
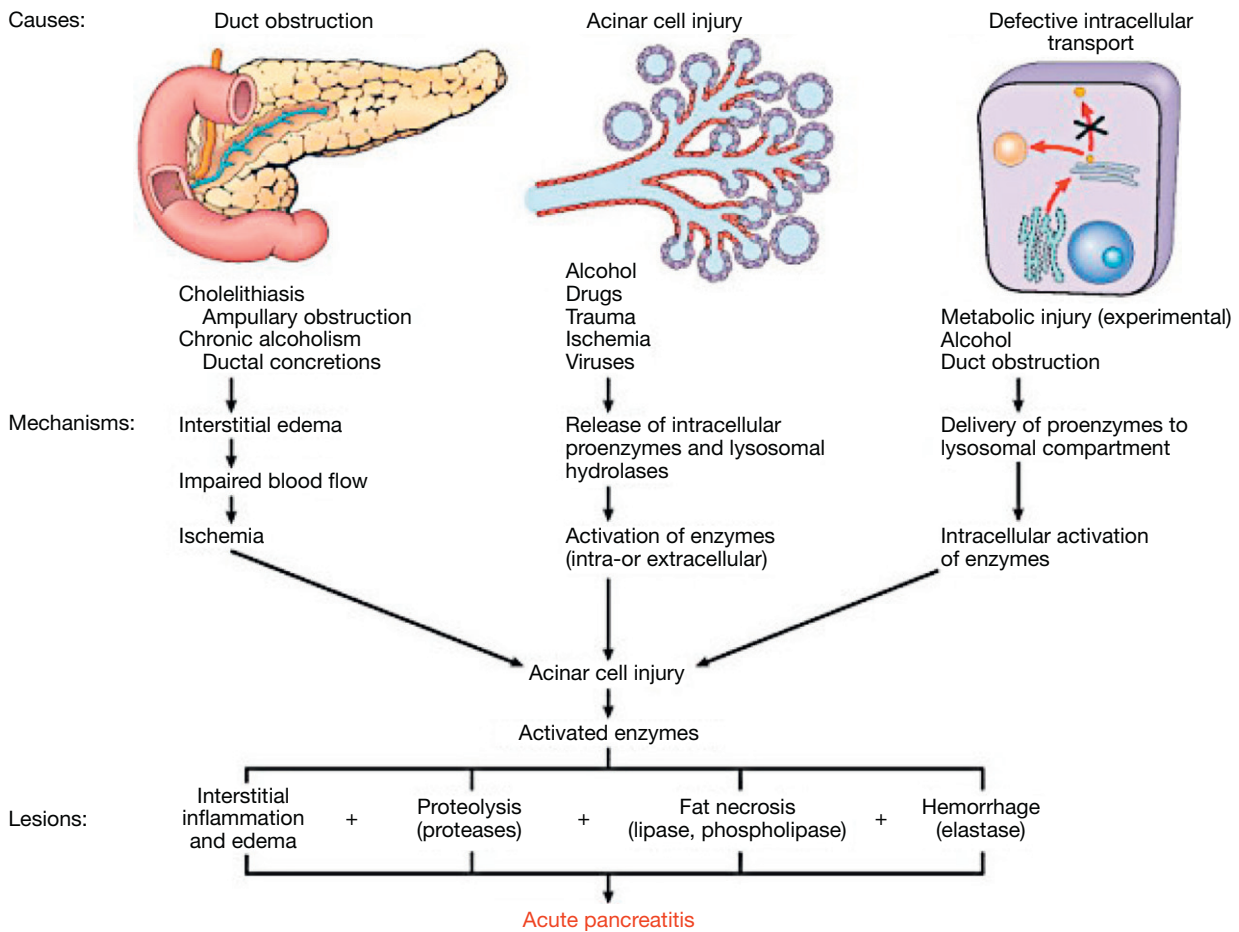

Figure 27   Three proposed pathways in the pathogenesis of acute pancreatitis. The inappropriate activation of pancreatic enzymes, especially trypsinogen, damages pancreatic parenchyma and potentiates further autodigestion. Reproduced from Robbins and Cotran, 2009. Pathologic Basis of Disease, eighth ed., p. 895.

with the immunosuppressive drug, azathioprine. Damage or disease of the biliary tree or obstructions of the pancreatic duct may cause pancreatitis. Mechanical injury to the pancreas may also incite pancreatitis, especially if there is damage to the ductal system. In small companion animal species, focal iatrogenic pancreatitis may result from biopsy or rough handling during laparotomy, or may be more widespread or regional after more intense trauma such as vehicle impact.

The pathogenesis of acute pancreatitis is complex and includes the intra-acinar activation of digestive enzymes resulting in degeneration and necrosis of acinar cells, leading to autodigestion of the pancreatic parenchyma and an intense concurrent inflammatory response. Damage to the acinar cells and cells lining the ductules and ducts is usually avoided because digestive enzymes are sequestered in membrane-bound intracytoplasmic vesicles and are produced as catalytically inactive proenzymes. It appears that events early in the process include the intra-acinar activation of trypsinogen and signaling in support of a local and systemic inflammatory cascade. The trigger for these processes is not known, but a variety of cellular mechanisms are likely involved, including altered calcium signaling, autophagy, and mitochondrial function (Figures 27–30).

A recently identified consequence of pancreatitis is damage to the intestinal mucosal barrier leading to translocation of gut microbes across the mucosa, resulting in sepsis and multiple organ failure. Pancreatitis may also predispose patients to the formation of thrombosis of splenic and portal veins. These complications are important causes of mortality among patients with acute pancreatitis.

Chronic fibrosing pancreatitis

Fibrosing pancreatitis is a chronic inflammatory process characterized by irreversible destruction of the architecture of the parenchyma and ductal system, with production of increased amounts of fibrous tissue. This chronic inflammatory process results in loss of both exocrine and endocrine functions. Dog breeds with increased risk of developing chronic pancreatitis are the Cavalier King Charles Spaniel, Collie, and Boxer.

Grossly, lobules are firm and white, with expansion of the interlobular stroma and thickening of the serosal tissues. Dystrophic mineralization may occur in parenchyma and adjacent mesenteric adipose tissue damaged by the release of pancreatic enzymes. The architecture of affected lobules is distorted by sheets and strands of fibrous tissue that dissect between and within affected regions, with marked distortion of acinar structure and compression of acinar cells. Abundant, paucicellular (mature) fibroplasia is often present around ducts, with hyperplasia of ductal epithelium and, sometimes, duct stenosis or luminal obstruction by condensed secretory material. The inter- and intralobular spaces and periductal adventitia are also infiltrated by varying numbers of neutrophils, lymphocytes, plasma cells, and macrophages (Figures 31–33).

In some lobules with early or mild fibrosis, ducts may be irregularly dilated and have flattened epithelial cells without microvilli; these changes probably reflect impaired secretion of anionic fluid, leading to precipitation and eventual inspissation of proteins secreted by acini and ultimately resulting in loss of secretory flow (Figure 34).

Figure 28 Pancreatitis and mesenteric steatitis in a 15-year-old, female-spayed, Beagle dog with concurrent lymphoma and massive hepatic necrosis. Multifocal to coalescing foci of inflammation and fat necrosis are present in the edematous mesentery. Image courtesy of Dr. Michael Yaeger, Iowa State University.
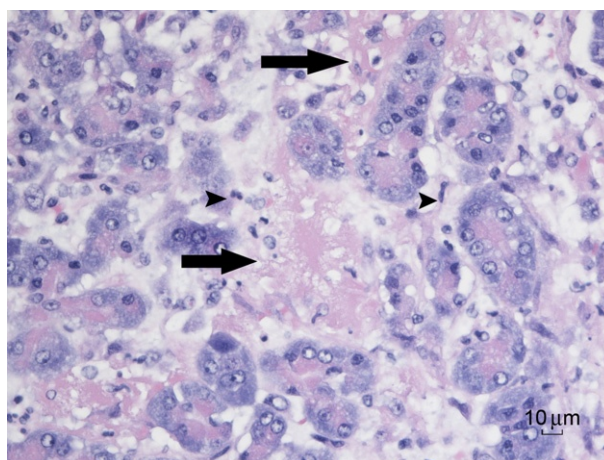

Figure 29 Early, acute, necrotizing pancreatitis. Within this lobule, there are multifocal to coalescing regions of acinar necrosis (arrows) characterized by loss of cellular detail and replacement by amorphous eosinophilic cell debris. A mild neutrophilic inflammatory infiltrate is present (arrowheads). Tissues are from a 9-year-old, male, Labrador Retriever dog.
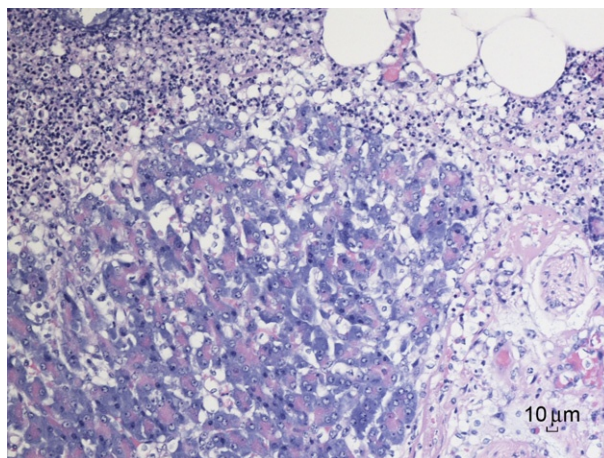

Figure 30 An intense suppurative inflammatory infiltrate expands the interlobular stroma, covers the peritoneal surface, and extends into this degenerating pancreatic lobule.
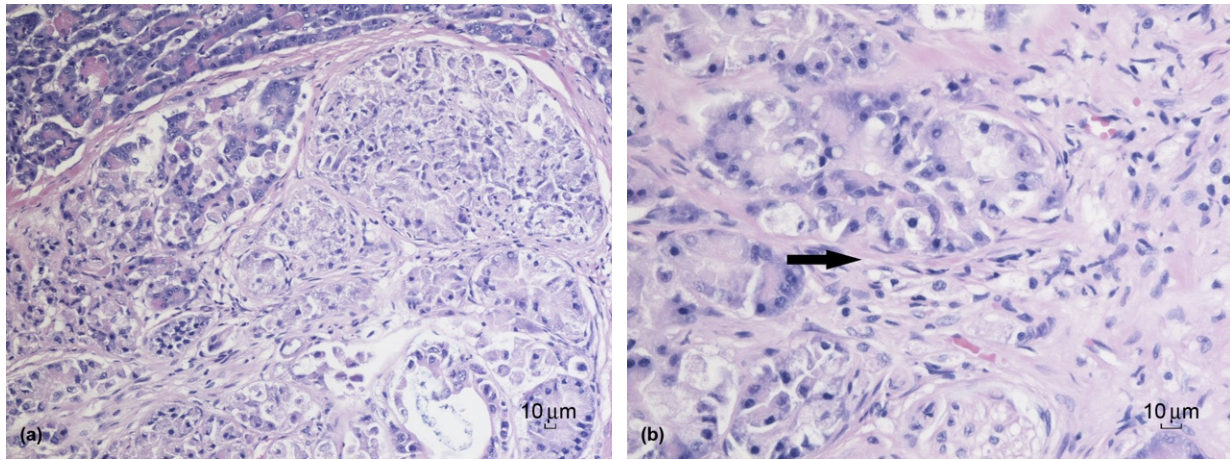
Figure 31   Mature fibrous tissue effaces the architecture of this pancreatic lobule (a). Strands of fibrous tissue (arrow) encircle and cause atrophy of several acini (b).
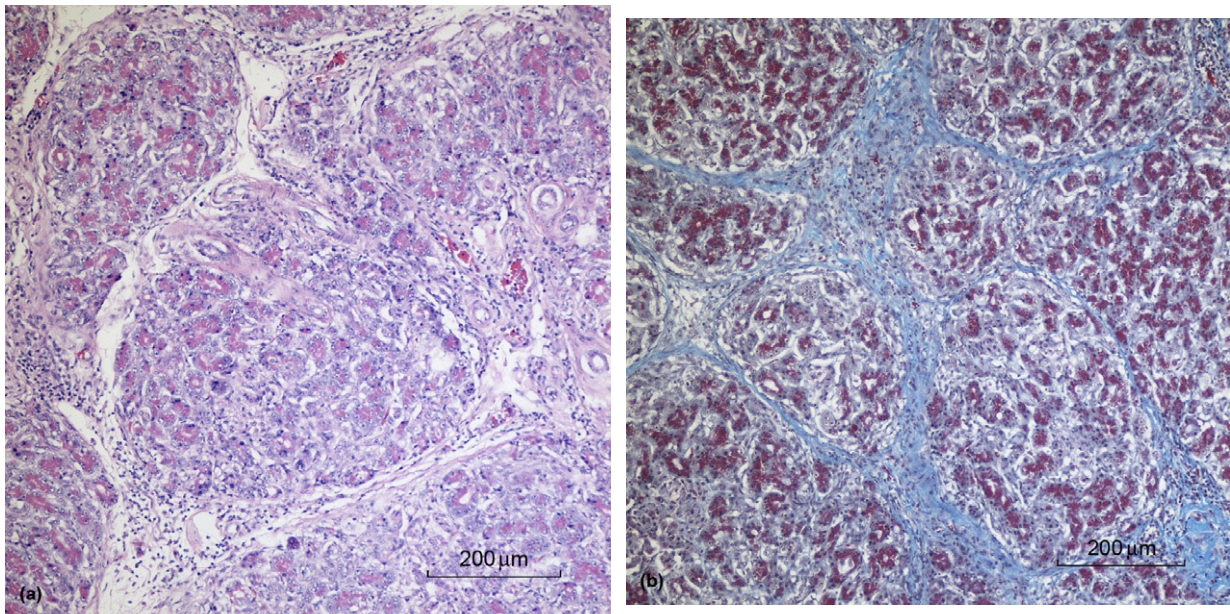

Figure 32   Mature fibrous tissue extends between and within lobules, resulting in atrophy of acini (a). Strands of collagen are highlighted by Masson's trichrome staining (b). Tissue from a 6-year-old, domestic short-haired cat.

Pancreatic Involvement in Systemic Diseases

The pancreas is susceptible to secondary damage by a wide variety of agents that impact this organ via direct, hematogenous, or ductular routes.

Multisystemic Eosinophilic Epitheliotropic Disease in Horses

Multisystemic eosinophilic epitheliotrophic disease (MEED) in horses is characterized by infiltration of eosinophils, CD3+ lymphocytes, and fewer plasma cells and the formation of eosinophilic granulomas in various internal organs, including

the pancreas and the skin. This condition has some similarity to hypereosinophilic syndrome of human beings. Clinical signs usually include weight loss and skin lesions, with or without fever. The cause of this syndrome is unknown, but suggested mechanisms include a hypersensitivity to intestinal parasites or other antigen resulting in secretion of interleukin-5 (Figure 35).

Disseminated Bacterial, Fungal, Parasitic, and Viral Diseases

A wide variety of bacterial, fungal, parasitic, and viral agents that cause systemic infections in animals have the potential to affect the pancreas. Highlighted here are a few examples of
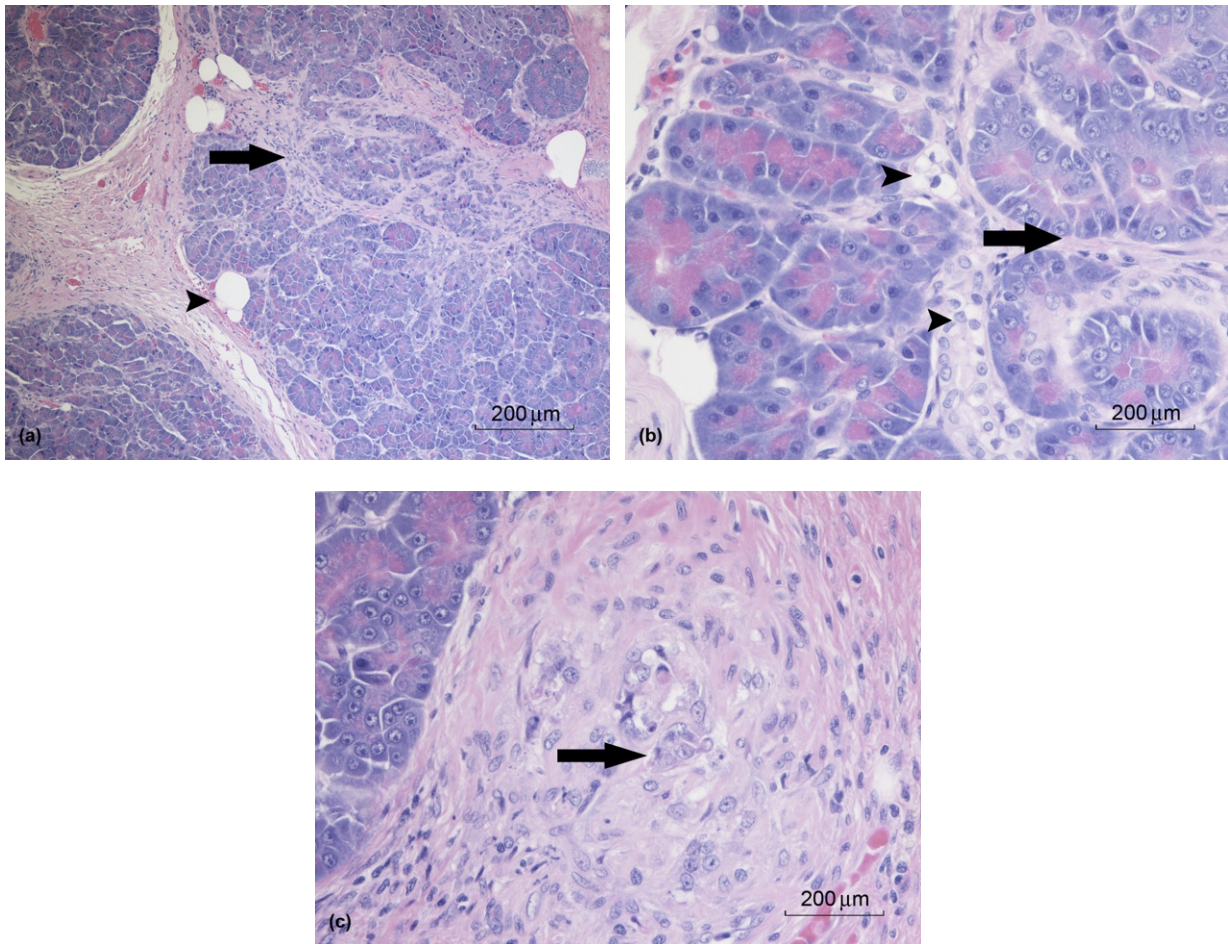
Figure 33 Chronic, fibrosing pancreatitis in a 13-year-old, male, Cavalier King Charles Spaniel dog with clinical signs of chronic pancreatitis, diabetes, and degenerative disk disease. Lobules of pancreatic parenchyma are separated and infiltrated by bands of variably mature fibrous tissue (arrow), with regional loss of acini and most islets (a). Scattered lipid-laden cells are present in the perilobular stroma (arrowhead) (b). Thin strands of fibrous tissue (arrow) separate atrophic acini. Islet cells and ductules have cytoplasmic vacuolation (arrowheads), consistent with concurrent diabetes. Fibrotic tissue has almost completely obliterated exocrine and endocrine elements of this lobule (c). A few residual cells (probably exocrine) remain (arrow). Case material courtesy of Dr. Michael Yaeger, Iowa State University.
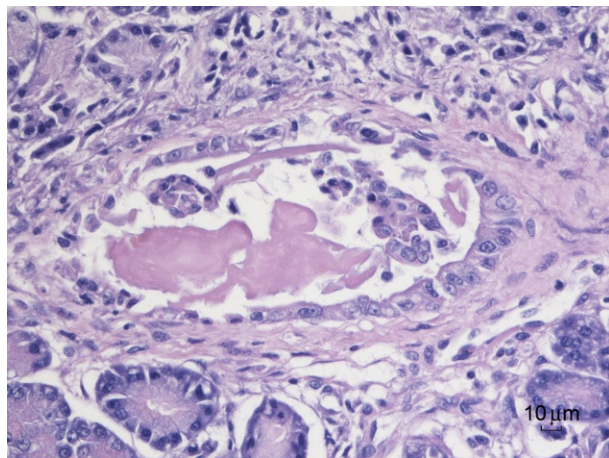

Figure 34 Damage to a ductule during pancreatic inflammation has resulted in degenerative changes to the ductular epithelium, resulting in loss of their secretory function and subsequent condensation of intraluminal proteinaceous secretory material. Atrophic ductular epithelial cells also have lost surface cilia, which also impairs luminal flow. There is mild adventitial fibroplasia and ongoing local acinar damage, indicating that this is a subacute to early chronic process in this image.
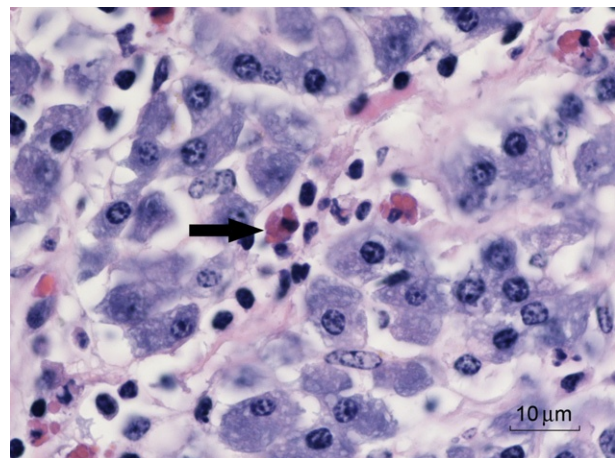

Figure 35 Eosinophils (arrow) infiltrate between acini containing atrophic and mildly autolytic acinar cells. Eosinophils of horses normally contain very large eosinophilic intracytoplasmic granules as demonstrated here.

infectious agents and animal species where pancreatic damage causes clinically important disease.

Endoparasites may cause disease by occluding pancreatic ducts or inducing an inflammatory response that causes periductal fibrosis. Pancreatitis secondary to endoparasitism is reported to be an important cause of death in free-ranging giant pandas. *Eurytrema* spp. flukes are common parasites of cattle in South America and Asia and may be found in primates, carnivores, pigs, birds, and other animals. Trematode eggs are common findings within the pancreatic parenchyma and other organs of many turtle species. Inflammatory responses surrounding the eggs are usually minimal.

Disseminated toxoplasmosis is an important cause of acute multifocal pancreatic necrosis in many mammals, especially
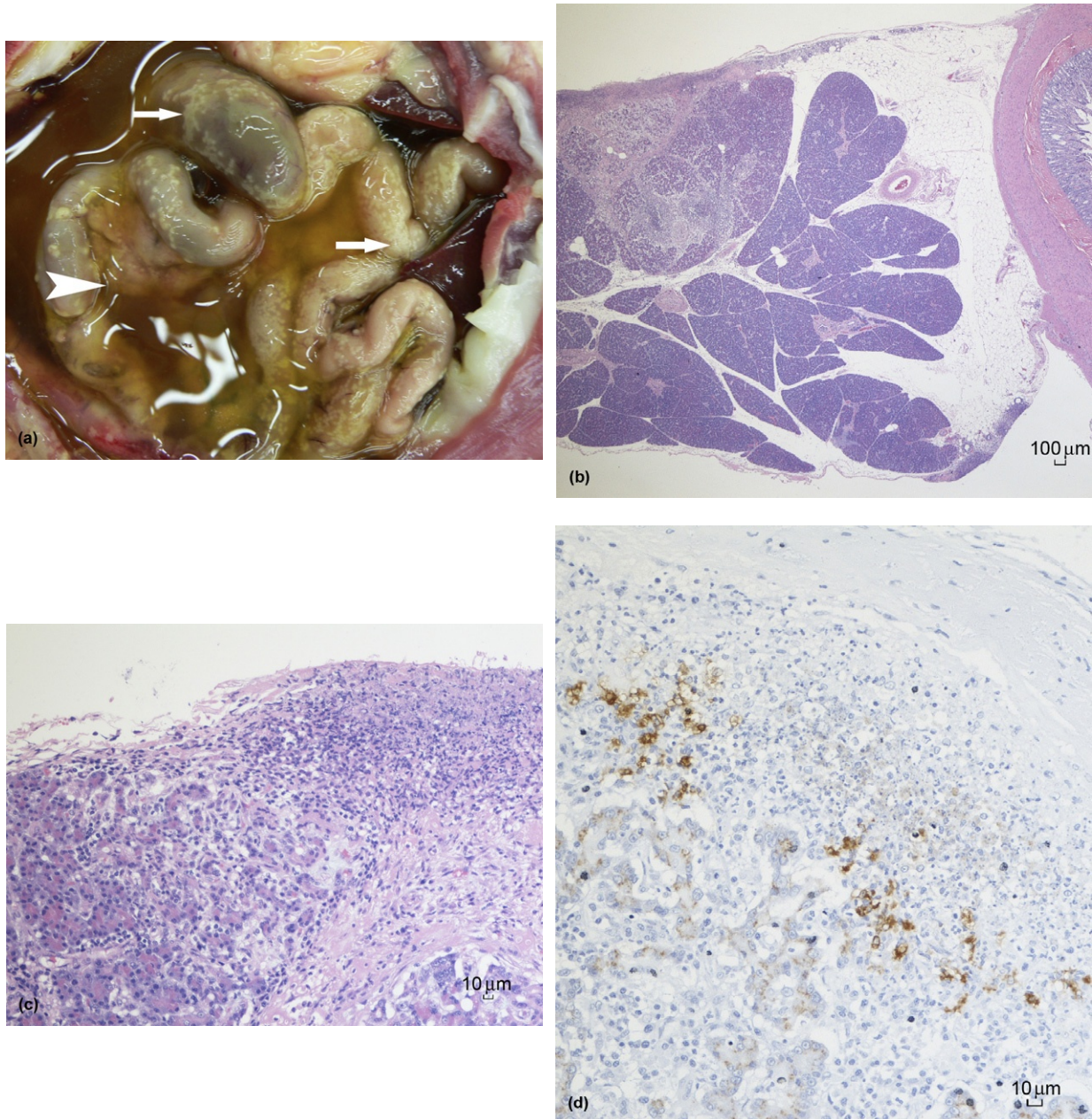

Figure 36   The pyogranulomatous inflammatory response in feline infectious peritonitis often affects the pancreas, contributing to clinical signs in this progressive, fatal disease of domestic cats caused by a variant feline coronavirus. Multifocal to coalescing fibrinous and pyogranulomatous inflammation (arrows; pancreas arrowhead) and an abundant, protein-rich effusion are present in the abdomen of a 1-year-old, female-spayed, domestic short-haired cat (a). Multiple lobules of the pancreas are infiltrated or replaced by inflammatory cells (b), (c). Immunohistochemical staining using antibody directed at porcine coronavirus (a related virus) demonstrates the presence of coronavirus antigens in inflammatory cells (d). Faint, nonspecific (background) staining is present in acinar cells. Diaminobenzidine chromogen and hematoxylin counterstain (d).

felines (domestic and exotic cats). *Toxoplasma gondii*, a zoonotic protozoan, may cause disseminated granulomatous and necrotizing inflammation in many organ systems.

Feline infectious peritonitis is a fatal disease of domestic cats that is caused by infection by a virulent feline coronavirus (FCoV). FCoV is a close relative to the human SARS coronavirus. Under some conditions, the host immune system mounts an intense response to FCoV antigens resulting in damage to serosal surfaces, including the mesentery, and widespread pyogranulomatous inflammation. Serosal damage may lead to accumulation of abundant protein-rich fluid in the abdomen. The pancreas frequently is affected, with multiple foci of surface and parenchymal damage (Figure 36).

Infection by ophidian paramyxovirus is an important cause of death in Viperidae snakes due to severe lung pathology. The pancreas and liver are also affected, with pancreatic acinar and ductal hyperplasia and intracytoplasmic inclusion bodies.

Metastatic Neoplasia

The pancreas is uncommonly the site of metastatic neoplasia. Effects of metastasis include replacement of pancreatic parenchyma by neoplastic tissue with loss of that functional capacity, as well as the potential for damage to the parenchyma or duct system with secondary pancreatitis. Hemangiosarcoma in dogs and, less frequently the visceral form in cats may undergo metastatic spread to the pancreas. The pancreas may be infiltrated widely by neoplastic lymphocytes in patients with disseminated lymphoma. Other systemic effects of neoplasia, such as metabolic imbalances, hypercalcemia, or prothrombotic conditions, may also affect the pancreas (Figures 37–39).

Toxins

The pancreas is a target organ for zinc toxicosis. Zinc toxicosis manifests as degeneration of acinar cells, without damage to cells in islets or forming exocrine ducts. Damage to acinar cells ranges from mi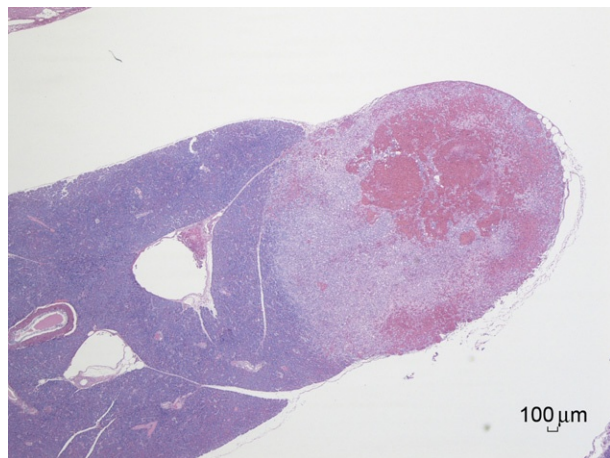ld atrophy with loss of zymogen granules to more severe loss of acinar architecture. Toxicosis is seen among diving ducks that swim on shallow bodies of water, such as those at fountains and parks, into which humans throw pennies containing zinc.

Diseases of the Endocrine Pancreas

Diabetes Mellitus

DM is a group of metabolic diseases characterized by abnormal glucose metabolism resulting in chronically elevated levels of blood glucose. The cause of DM in humans and animals appears to be a complex interplay between genetic and epigenetic (environmental) factors. Two basic underlying mechanisms reflect the different forms of the disease, namely, defects in production of insulin by the pancreas (type 1 DM) and resistance by target cells to the effects of insulin coupled with abnormal secretion of insulin (type 2 DM). In addition, metabolic changes during pregnancy are sometimes related to the development of elevated levels of blood glucose and are termed 'gestational diabetes.' There are important differences in the incidence, pathogenesis, and consequences of this disease among animal species, although similarities to the disease in human beings exist. Risk factors include increasing age. Obesity is important in some animals (cats), whereas it does not appear to predispose others (dogs) to developing DM. Diabetes and metabolic syndrome resulting from insulin resistance is being recognized as an important disease in horses. The incidence of reporting of DM among exotic animals is increasing, probably due to enhanced medical care of these animals. Reports of DM among livestock are unusual, perhaps due to population dynamics and economic considerations.

In contrast to cats that develop type 2 DM most frequently, domestic dogs with DM have underlying destruction of beta

Figure 37   Hemangiosarcoma, a malignancy of endothelial cells common in dogs, effaces local pancreatic parenchyma in this image. Similar masses composed of neoplastic endothelial cells forming blood-filled channels were widely disseminated throughout the body of this dog.

Figure 38   Multiple nodules of neoplastic lymphocytes, grossly evident as soft, white masses (arrows), infiltrate pancreatic parenchyma in the pancreas of a 10-year-old, female-spayed, Siamese cat with disseminated T-cell lymphoma. Multiple nodules of nodular hyperplasia (arrows; grossly indistinguishable from lymphoma) and regions of chronic, periductal inflammation also are present. Abundant adipose tissue is present in the mesoduodenum (star). Case material courtesy of Dr. Ronald Myers, Iowa State University.
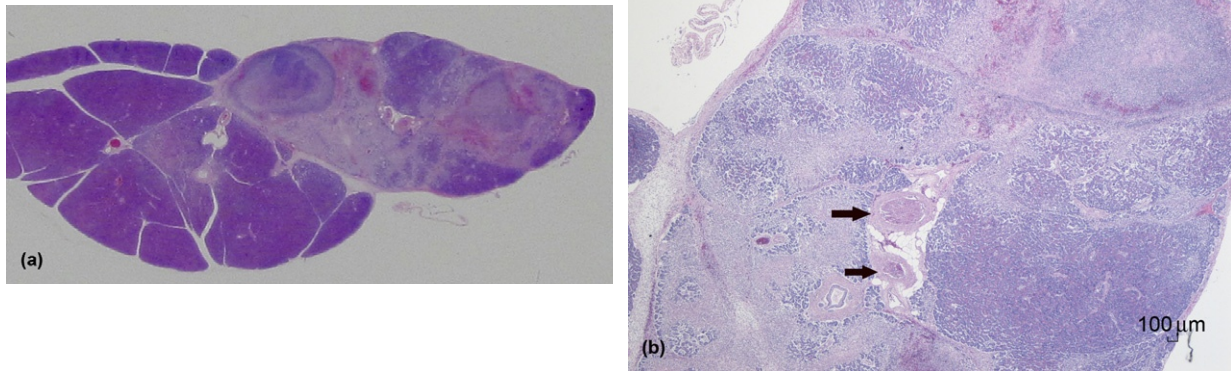
Figure 39   Lobular infarction. Organizing vascular thromboembolism associated with disseminated histiocytic sarcoma has resulted in locally extensive necrosis, suppurative inflammation, and mild hemorrhage of pancreatic lobules (a), (b). Tissue from a 15-year-old, male, German Short-haired Pointer dog.

cells with permanent loss of the ability to produce insulin. It is usually a slowly progressive disease that affects older adult dogs. The association of a specific DLA haplotype has been associated with the development of DM in dogs and is common in dog breeds that have increased incidence of DM (Samoyed, Cairn Terrier, and Tibetan Terrier) and reduced incidence in dog breeds that are relatively resistant to DM (Boxer, German Short-haired Pointer, and Golden Retriever). Pathogenic mechanisms associated with DM in dogs appear to be centered on the development of autoimmunity, with reports of autoantibodies to insulin and other islet antigens, similar to latent autoimmune diabetes in human beings.

Domestic cats with DM usually have features most consistent with type 2 DM of human beings, sometimes with histological features consistent with concurrent pancreatitis. Besides domestic short- and long-haired cats in which the disease is common, some populations of Burmese cats have increased risk of developing type 2 DM. In addition, cats sporadically present with hyperglycemia due to causes that would be classified as 'other specific types' under the human classification scheme.

Obesity, the accumulation of excess amounts of lipid within adipocytes and associated metabolic, inflammatory, and hormonal changes, has reached epidemic proportions among companion animals (dogs and cats) and to a lesser extent among horses in Western countries, similar to the situation in human beings. Obesity-induced insulin resistance occurs in dogs, cats, and horses, but dogs have not been documented to progress from this state to type 2 DM. Obese dogs do have elevated postprandial levels of insulin, glucose, and triglyceride, but members of a small cohort of obese dogs followed for several years did not develop clinical signs of DM. Dogs maintain high fasting concentrations of insulin in order to compensate for insulin resistance and are able to maintain normal blood glucose levels. Leptin, a hormone involved in monitoring energy levels in the body and produced in the white adipose tissue, appears to be involved in this compensation, as serum levels are elevated in obese dogs with insulin resistance.
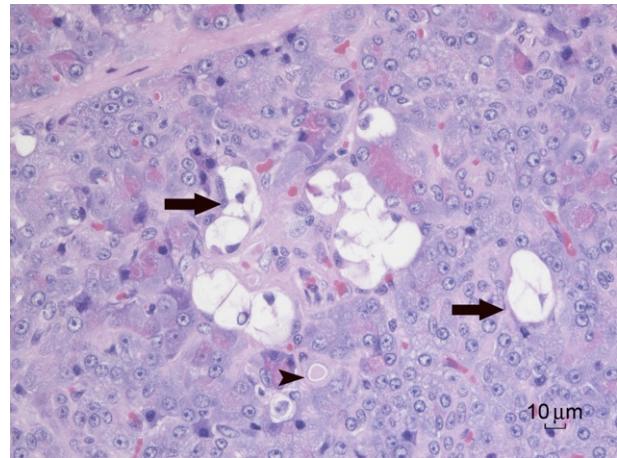

Figure 40   Cells in the islets of this 10-year-old, male-neutered, domestic long-haired cat with DM and chronic pancreatitis exhibit marked cytoplasmic vacuolation (arrows). Acinar cells are atrophic, with few intracytoplasmic zymogen granules. Focally, a ductule (arrowhead) is dilated by secretory material. Case material courtesy of Dr. Amanda Fales-Williams, Iowa State University.

Microscopic changes that support a diagnosis of DM include loss of islets, infiltration of islets by inflammatory cells, and marked cytoplasmic vacuolation of islet cells. Ductular epithelium often has basally located intracytoplasmic vacuoles. In cats and cynomolgus macaques, deposition of amyloid in islets is common. The development of amyloidosis of the islets is almost universal in type 2 DM in human beings and cynomolgus macaques and is also a common finding in wild and domestic felids with this disease. It is, however, also present at a low incidence in some clinically normal cats, so it is not pathognomonic for type 2 DM in cats. The deposition of amyloid occurs due to altered beta-cell function whereby overproduction of amylin (islet amyloid polypeptide) results in the formation of amyloid fibrils. Other aspects of altered beta-cell function are believed to accompany the overproduction of amylin (**Figures 40–42**).

Neoplasia of Pancreatic Islet Cells

Tumors may arise individually in each of the endocrine cell populations in the pancreas, sometimes with overproduction of an endocrinologically active hormone such as somatostatin, pancreatic polypeptide, and others. Excess levels of a tumor-secreted hormone usually result in disrupted homeostasis. The most common tumors arising in islet cell populations that are clinically evident, and therefore diagnosed, are benign or malignant neoplasms of the beta cell.
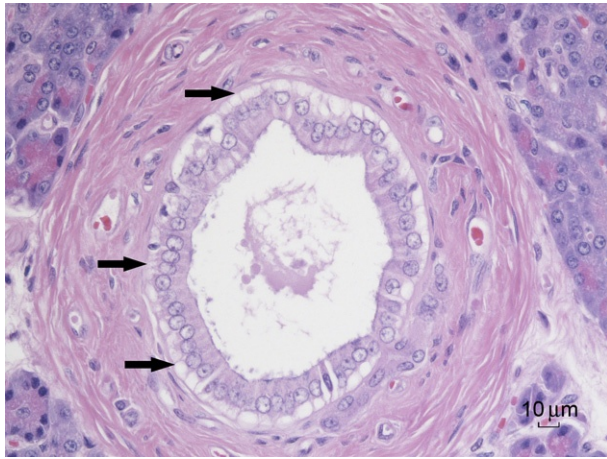

Figure 41   Cells lining this interlobular duct of a 10-year-old, male-neutered, domestic long-haired cat with type 2 DM and chronic pancreatitis have prominent, basilar, intracytoplasmic vacuoles (arrow). Case material courtesy of Dr. Amanda Fales-Williams, Iowa State University.

Insulin-secreting beta-cell tumors

Neoplasms arising from a beta cell that has retained the ability to produce insulin are termed a 'functional' beta-cell tumor. These neoplasms are hormonally active and may secrete high concentrations of insulin, which result intermittently in marked hypoglycemia, due to insulin-induced uptake of glucose by target cells of the body. Although not specific for these neoplasms, episodic and progressively severe clinical signs associated with hyperinsulinism include hindlimb weakness, exercise intolerance, ataxia, reduced mental capacity, and, late in the disease, seizures.

Adenomas and carcinomas arising from beta cells are the most frequent type of endocrine tumor of the pancreas, with carcinomas reported to be more common than adenomas in dogs. Dog breeds with an increased incidence of beta-cell tumors include Boxers, Fox Terriers, Standard Poodles, and German Shepherds. Beta-cell tumors, 'insulinomas,' are common in ferrets and have been reported occasionally in other animal species. The nomenclature used to describe benign versus malignant and productive versus nonproductive tumors seems to vary between veterinary clinicians and pathologists, so 'insulinomas,' that is, insulin-producing beta-cell tumors, usually have a malignant clinical course, with frequent metastasis outside the pancreas.

Macroscopically, adenomas and carcinomas of the islets usually have a similar color and consistency to the surrounding pancreatic parenchyma. Adenomas are usually small, well-demarcated nodules confined by a connective tissue capsule, while carcinomas are larger and have very invasive growth characteristics, invading into the adjacent parenchyma, migrating within lymphatic vessels, and forming secondary tumors in distant sites. Functional islet tumors producing severe clinical signs may be small and difficult to identify.
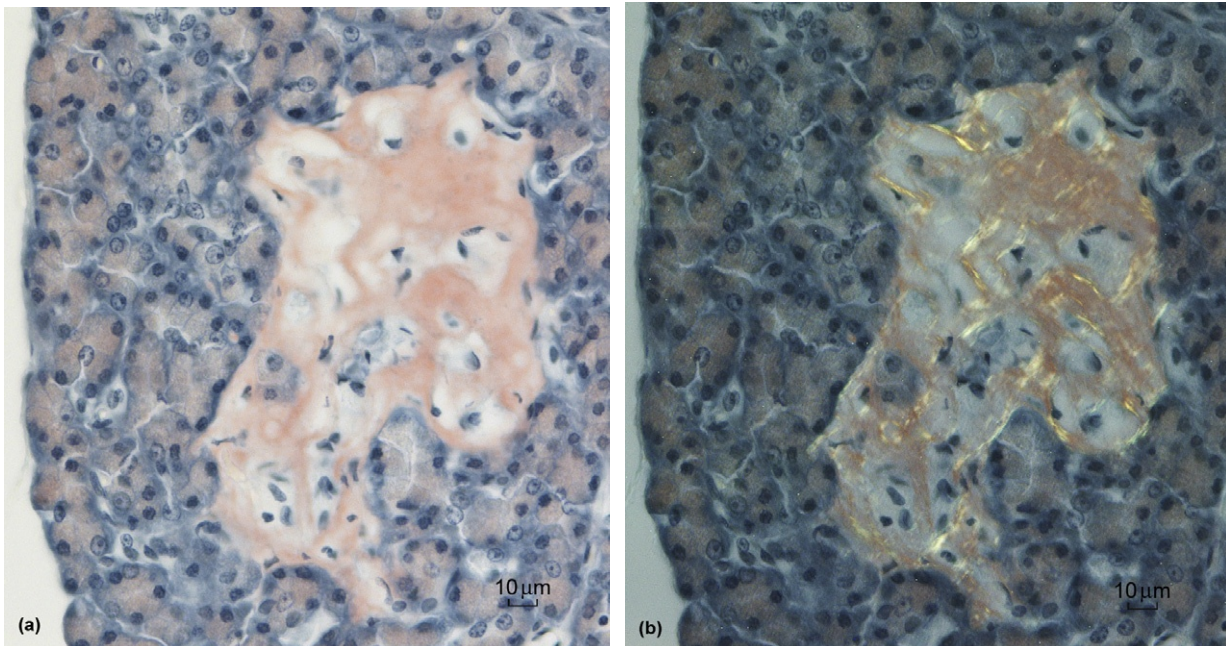

Figure 42   Insular accumulation of amyloid is a common finding in cats with DM (homologous to human type 2 DM). This material (red orange in this Congo Red-stained section (a)) is derived from islet amyloid polypeptide (amylin), a hormone secreted by beta cells of the islet. Amyloid fibrils have apple green birefringence under polarized light (b).
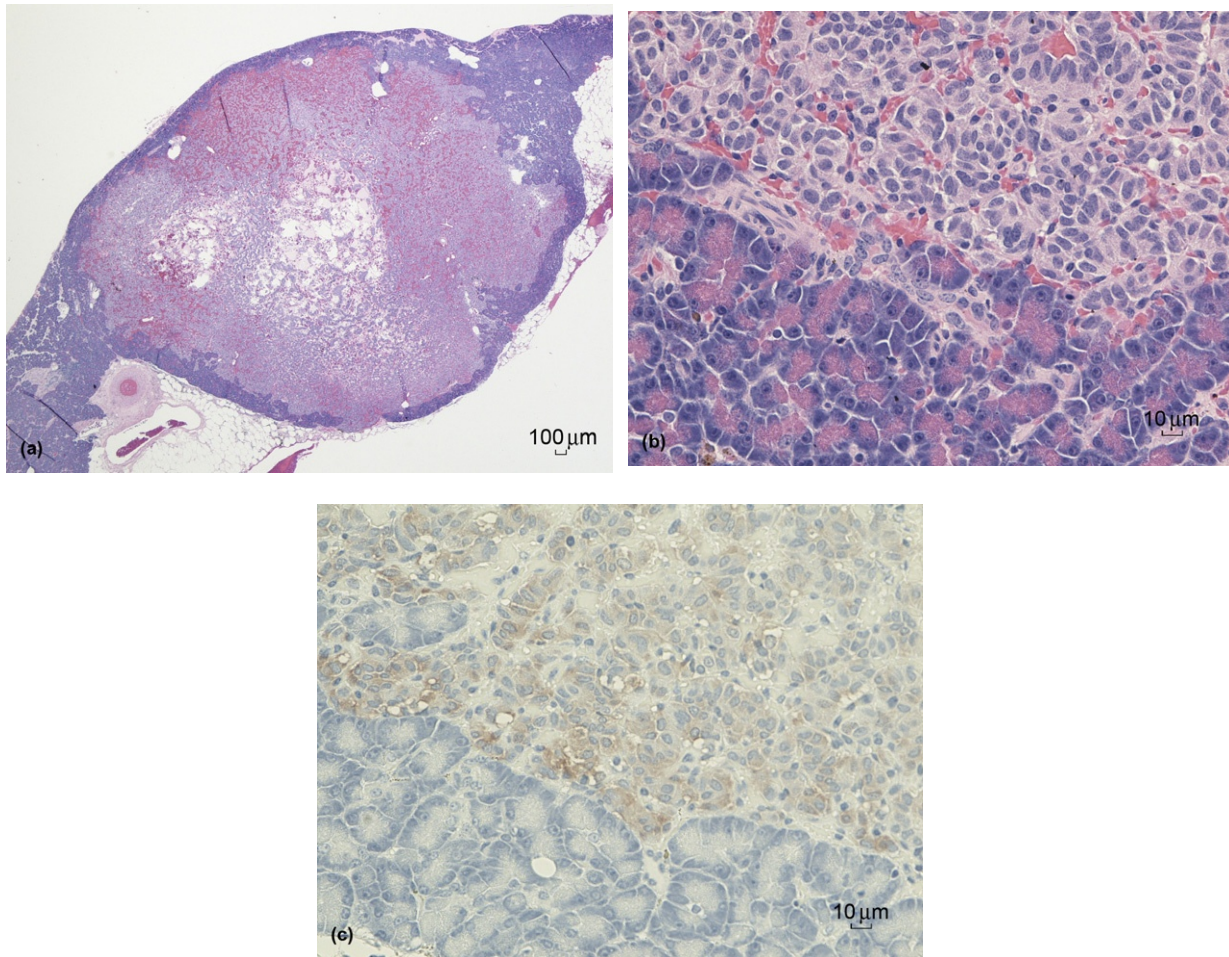
Figure 43   This section of the pancreas from a 5-year-old, male, European ferret contains a poorly demarcated, expansile, and mildly infiltrative neoplasm (a) composed of groups of beta cells supported by fine strands of fibrovascular tissue (b) and demonstrating immunoreactivity to insulin (c). Diaminobenzidine chromogen and hematoxylin counterstain (c).

Cells comprising beta-cell tumors usually resemble their normal counterparts in islets. Individual cells have indistinct cell borders and are cuboidal to columnar with lightly eosinophilic and finely granular cytoplasm. Cells in carcinomas have more features of anaplasia, including anisocytosis and anisokaryosis. Mitotic figures are not frequent. Scattered within many adenomas are groups of cells with acinar or ductular differentiation. The presence of these cells probably represents the common histogenesis of endocrine and exocrine elements of the pancreas (**Figure 43**).

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http://www.offa.org/about.html – Orthopedic Foundation for Animals – repository for genetic diseases of animals.

http://www.umass.edu/vetimm/ – U.S. Veterinary Immune Reagent Network – repository for information regarding genes, antibodies, and cytokines for veterinary species.