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CHAPTER

9

Ferret gastrointestinal and hepatic diseases

Mark E. Burgess

'Whenever you find yourself on the side of the majority, it is time to pause and reflect.'

Mark Twain

Introduction

The ferret gastrointestinal (GI) tract is short and fairly simple, typical of a carnivore digestive system. It comprises a simple stomach, duodenum, 'jejunoileum' (jejunum and ileum are indistinguishable), and colon. Ferrets lack a caecum or ileocolic junction. The normal gastrointestinal transit time is rapid, varying from 148 to 219 min.[1]

The ferret gut is also extremely reactive and commonly demonstrates a strong inflammatory response from a variety of aetiologies. Chronic gastroenteritis is common, and in the author's experience often results in clinical disease, or in alterations of gut function, such as delayed gastric emptying and greatly slowed gastrointestinal transit times.

Our understanding of the pathophysiology of the common gastroenteropathies in ferrets is incomplete. Two factors have slowed our recognition and understanding of ferret gut pathology. First, many ferrets with chronic gastroenteritis demonstrate only subtle signs of illness which are often overlooked. Second, there are commonly held misconceptions regarding ferret gastroenteric disease, which persist despite considerable histopathologic evidence which should force us to rethink some of the current views of the ferret gut. This chapter is an attempt to present ferret gastrointestinal (and hepatic) diseases in a logical and practical format, emphasizing those diseases with high clinical relevance, and de-emphasizing some diseases which have received much attention to date but which may be clinically less important.

Overview of gastrointestinal disease (cranial to caudal)

- Oral ulcers
- Megaoesophagus
- Gastric foreign bodies and trichobezoars
- Gastric ulcers
- *Helicobacter* gastritis
- Inflammatory bowel disease
- Intestinal foreign bodies
- *Coccidia*
- Coronavirus enteritis (ECE)
- Eosinophilic granulomatous disease
- Bacterial overgrowth/enteritis
- Enterotoxaemia
- Aleutian disease virus
- Neoplasia: lymphoma, pancreatic adenocarcinoma, etc.
- Proliferative bowel disease
- Proctitis.

Overview of GI disease based on clinical incidence

Diseases with high clinical incidence:

- Oral ulcers
- Gastric and intestinal foreign bodies, trichobezoars
- Coronavirus enteritis (ECE)

- Inflammatory bowel disease
- Bacterial overgrowth/enteritis
- Gastric ulcers.

Diseases with moderate clinical incidence:

- Proctitis
- Neoplasia
- *Helicobacter* gastritis.

Diseases with low clinical incidence:

- Megaoesophagus
- Aleutian disease virus (causing GI signs)
- Enterotoxaemia
- Proliferative bowel disease
- Coccidiosis
- Eosinophilic granulomatous disease.

Overview of hepatic diseases

- Lymphocytic hepatitis
- Suppurative hepatitis
- Hepatic lipidosis
- Vacuolar hepatopathy
- End stage liver disease (cirrhosis)
- Biliary cysts
- Metastatic neoplasms
- Primary hepatic neoplasms.

Clinical findings associated with various gastrointestinal disorders

- *Nausea* (bruxism, pawing at mouth, salivation, vomition): gastric foreign body, trichobezoar, gastric ulcer, inflammatory bowel disease, bacterial overgrowth and/or enteritis, coronavirus enteritis (first 48 h), intestinal foreign body, intestinal lymphoma, *Helicobacter* gastritis. Eosinophilic granulomatous disease (uncommon) and proliferative bowel disease (rare) may produce nausea
- *Regurgitation* (ejection of food within 5 min postprandial, with minimal nausea; patient often eats after regurgitating): megaoesophagus
- *Anorexia*: nearly any gut lesion may produce this sign
- *Diarrhoea* (greenish, or brown, or mucoid, or loose 'birdseed' stools): bacterial overgrowth and/or enteritis (often greenish, often mucoid), coronavirus enteritis (bright green, may fade to brown with antibiotic therapy), inflammatory bowel disease (greenish to brown, mucoid to birdseed). *Note*: bacterial enteropathies may occur secondary to sudden diet changes, dietary indiscretion, or secondary to nearly any other intestinal lesion, such as inflammatory bowel disease, coronavirus enteritis, or intestinal lymphoma. Uncommon diseases that may produce diarrhoea include eosinophilic granulomatous disease and proliferative bowel disease
- *Weight loss/muscle wasting* despite good appetite: inflammatory bowel disease, bacterial overgrowth/enteritis, coronavirus enteritis, intestinal lymphoma. Eosinophilic granulomatous disease (uncommon) and proliferative bowel disease (rare) may cause wasting
- *High fever*: acute bacterial enteritis and/or hepatitis (often secondary to underlying gut pathology), septicaemia (secondary to severe gastroenteritis), acute coronavirus enteritis or perforated gastrointestinal ulcer with septic peritonitis
- *Melaena* (acute or chronic): gastric or duodenal ulcers, gastric foreign body, inflammatory bowel disease, *Helicobacter* gastritis, gastrointestinal lymphoma
- *Proctitis* (red, swollen anal mucosa): secondary to any chronic enteropathy, especially with chronic diarrhoea; e.g. inflammatory bowel disease, coronavirus enteritis, bacterial overgrowth
- *Palpable thickened bowel*: intestinal lymphoma, eosinophilic granulomatous disease (uncommon), proliferative bowel disease (rare)
- *Palpable mesenteric lymphadenopathy*: intestinal lymphoma, inflammatory bowel disease, eosinophilic granulomatous disease (uncommon), proliferative bowel disease (rare)
- *Tenesmus*: inflammatory bowel disease with colitis, bacterial overgrowth/enteritis, intestinal lymphoma, eosinophilic granulomatous disease (uncommon), proliferative bowel disease (rare)
- *Rectal prolapse*: (a) Mild: inflammatory bowel disease, bacterial enteritis/colitis, intestinal lymphoma, eosinophilic granulomatous disease (uncommon). (b) Severe: proliferative bowel disease (rare), or other severe colonic pathology, e.g. severe colitis, intestinal lymphoma (all rarely cause severe prolapse)
- *Leukocytosis*: may be seen with most gut pathology, especially if secondary bacterial overgrowth or enteritis occurs
- *Eosinophilia*: inflammatory bowel disease (occasionally); eosinophilic granulomatous disease (uncommon disease, but eosinophilia is common with this disease)

- *Neutrophilia*: bacterial overgrowth and/ or enteritis, often secondary to underlying gut pathology such as inflammatory bowel disease, coronavirus enteritis, intestinal lymphoma, eosinophilic granulomatous disease. Intestinal foreign bodies may also produce neutrophilia, especially with bowel necrosis and/or rupture
- *Lymphocytosis*: inflammatory bowel disease, intestinal lymphoma, possibly *Helicobacter* (uncommon).

Gastrointestinal diseases (cranial to caudal)

Oral ulcers

Oral ulcers commonly occur on the palate secondary to self mutilation (pawing at the mouth with the forepaws). These are usually circumscribed, shallow oval to round red ulcers on the palate (cranial or caudal), 3–10 mm in diameter. Pawing at the mouth is common in ferrets with gastrointestinal disease causing nausea or abdominal pain; it is also common with administration of foul tasting medication, e.g. metronidazole.

Treatment includes identifying and correcting the underlying cause (e.g. gut lesions, medications) and trimming the front toenails short. Sucralfate (Carafate) suspension 100–125 mg orally may adhere to the ulcer; oral antibiotics may be used to minimize secondary infection.

Prevent iatrogenically induced ulcers by restraining the ferret during and after medicating; administer a sweet liquid such as a sugary syrup immediately before and after giving a foul or bitter tasting drug.

Megaoesophagus

An infrequent disease in ferrets, its etiology is poorly understood in many cases.[2,3] It appears to be an acquired, not congenital condition. We have histopathologically linked some cases to underlying gastritis with associated gastric acid reflux and oesophagitis.[4]

Signs include distress while eating, choking/coughing, extending the neck postprandially, and regurgitation within 5–10 min (or sooner) postprandial. Neck palpation sometimes reveals fluid and gas distension of the proximal oesophagus, on the left side of the neck just caudal to the head. Radiographs may show retained air or food in the oesophagus. Radiographic diagnosis is enhanced by administering a barium swallow mixed with food, followed by an immediate radiograph; findings typically are a dilated cervical and thoracic oesophagus with retained food and barium (Ch. 16).

Treatment may be unrewarding if oesophagitis is not involved. Cisapride dosed at 0.5 mg/kg p.o. b.i.d. has produced minimal benefit in our patients. For cases with reflux oesophagitis, total resolution of signs can sometimes be achieved via administration of acid blockers such as ranitidine (Zantac) or famotidine (Pepcid). We have had more experience using ranitidine; our usual dose is 3.5 mg/kg p.o. b.i.d. for several weeks, possibly long term. Sucralfate (Carafate) suspension may be administered at 100–125 mg per ferret p.o. b.i.d./t.i.d.; this may adhere to both gastric and oesophageal ulcerations and aid healing. Metoclopramide (Reglan) may be used to encourage gastric emptying and reduce reflux; typical dosing is 0.5–1.0 mg/kg p.o. b.i.d.

Feed liquefied food such as Hill's a/d gruel; elevate the front of the ferret's body while eating (one may place food on an elevated platform). Patients with reflux oesophagitis that respond well to acid blockers may eventually be returned to a normal diet. Underlying gut pathology should be identified and addressed when the patient is stabilized. Rarely reflux oesophagitis may lead to distal oesophageal stricture; prognosis in these patients is grave.

Gastric foreign bodies and trichobezoars

These are seen in any age animal. Ingested rubber materials and trichobezoars are common. Affected ferrets are often asymptomatic; signs can include vomition, anorexia, melaena, lethargy, weight loss, bruxism or pawing at the mouth. Subclinical cases may still develop gastritis (see Inflammatory bowel disease comments).

Palpation may discern the foreign body, but clinicians may find that the stomach rests too far cranially (between the ribs) for easy palpation. Radiographs with a barium swallow may or may not visualize the object; even trichobezoars often fail to retain barium due to their smooth dense composition and mucus-coated surface (Ch. 16). An air contrast gastrogram may aid visualization. Serum chemistries may show elevated lipase (over 500 IU/L at commercial veterinary diagnostic laboratories,[5,6] or over 1000 IU/L using an in house IDEXX VetTest® machine[7] – see Inflammatory bowel disease discussion), as well as elevated globulin (over 3.0 g/dL).[8]

Prevent foreign bodies by severely restricting access to ingestible items, especially those with a soft rubbery texture. Prevent trichobezoars by brushing moulting animals, and using a feline hairball laxative in moulting animals and other animals deemed to be at risk (such as cage mates who groom the moulting ferret, or ferrets with a prior history of trichobezoars). Ferrets with

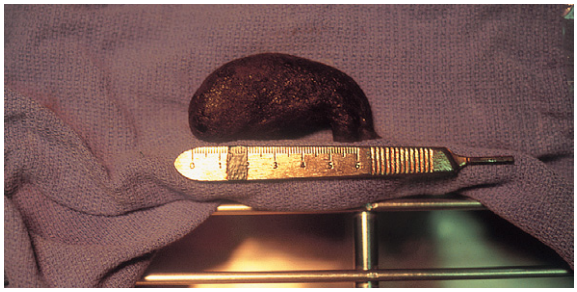

Figure 9.1 An unusually large trichobezoar which filled the stomach of the affected ferret.

significant gastritis may exhibit reduced gastric motility and a potentially higher risk for hair retention (see Inflammatory bowel disease).

Treatment of gastric foreign bodies and trichobezoars is usually via gastrotomy; endoscopic removal is possible with smaller objects. The small bowel does not allow passage of any but the smallest objects, so removal is usually required. Trichobezoars in ferrets are usually too dense and firm to dissolve with medications, and too large to pass though the bowel even with lubricants. Figure 9.1 shows an unusually large trichobezoar which filled the stomach of the affected ferret. A gastrotomy or enterotomy in this species may be treated with 7 days of postoperative antibiotics, such as enrofloxacin 5 mg/kg p.o. b.i.d. plus amoxicillin 10 mg/kg p.o. b.i.d.

Gastric palpation is recommended during any laparotomy procedure; incidental gastric foreign bodies are common findings and should be removed when detected (Ch. 18).

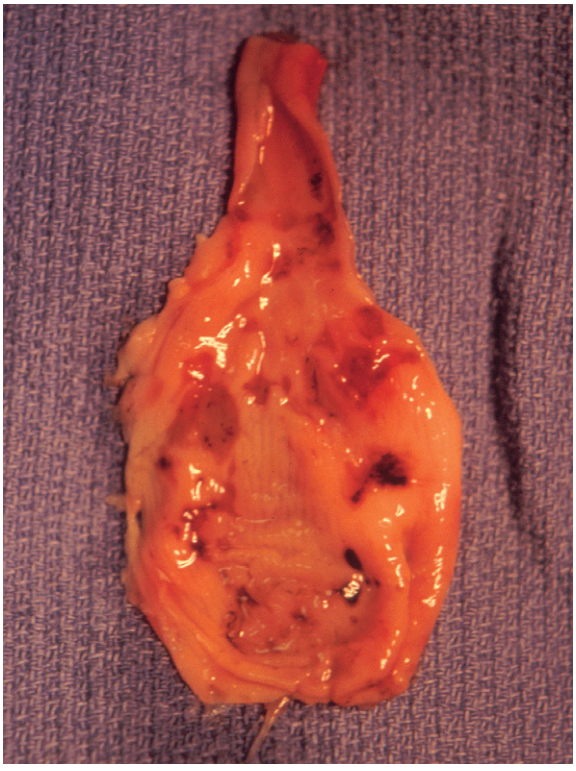

Figure 9.2 A necropsy specimen of stomach and proximal duodenum, showing severe gastric ulcerations. This patient died from blood loss associated with haemorrhage from the ulcers. *Helicobacter* was not detected histopathologically.

Gastric ulcers

Ferrets have been described as being prone to gastric ulcers secondary to various factors,[9] including azotaemia, ulcerogenic drugs, foreign bodies, and *Helicobacter* overgrowth.[10,11,12] Many of our patients with ulcers have concurrent generalized gastroenteritis (inflammatory bowel disease). Signs may include melaena (tarry stools), anorexia, vomition, bruxism and weight loss. In extreme cases, gastric or duodenal ulcers can rupture a blood vessel and cause severe prolonged bleeding, leading to anaemia or shock. Severe ulcers can occasionally perforate the gut, leading to septic peritonitis and death if not corrected. Figure 9.2 shows a necropsy gastric specimen with numerous severe ulcerations.

Any patient with signs of GI ulcers should ideally have a blood profile evaluated, and if evidence of chronic gut inflammation is present (e.g. elevated serum lipase or globulin), gut biopsies should be recommended when the patient is stable. Any unrecognized foreign bodies would also be detected during a biopsy procedure (Ch. 18). Histopathology is typically required to definitively identify an underlying gut disorder, such as inflammatory bowel disease, *Helicobacter* gastritis, lymphoma, etc.

More conservative treatment would include an acid blocker such as ranitidine (Zantac), famotidine (Pepcid), or omeprazole (Prilosec). See *Helicobacter* gastritis for drug doses. In addition, sucralfate (Carafate) may be used to aid ulcer healing, at 100–125 mg/ ferret p.o. b.i.d./t.i.d. for 5–7 days or until signs resolve. Ideally give sucralfate on an empty stomach (no food or other drugs present). Sucralfate may bind to food or other medications, reducing its binding to ulcerated mucosa, and reducing absorption of other medications. Trial therapy for *Helicobacter* infection could be initiated (see *Helicobacter* gastritis). Alternatively, enrofloxacin 5–10 mg/kg p.o. b.i.d. plus amoxicillin 10–20 mg/kg

p.o. b.i.d. can be used to control a bacterial overgrowth or enteritis in the small bowel (in the event that melaena is arising from hemorrhagic enteritis and not a focal ulcer).

Helicobacter gastritis

Helicobacter mustelae is a spirilliform bacterium that lives in the stomach (primarily the pyloric region) and first 1 cm of the duodenum in the ferret. Research models have promoted *Helicobacter* as a significant gastric pathogen in the domestic ferret, based on its ability to produce lesions in controlled research settings. [10,11,12,13,14] These studies have shown that *Helicobacter* is common in the ferret stomach and may be nearly ubiquitous in the domestic ferret population, at least in the USA. Typically, when an organism is so universally distributed in a host population, it is well host-adapted and tends to behave as 'normal flora' in most situations. Our clinical experience supports this; *Helicobacter* appears to have low pathogenicity in most of our ferret patients; in some cases, it may produce a mild to severe lymphoplasmacytic gastritis. Prior authors noted clinical disease occurring mostly in 3–5-month-old stressed ferrets.[15] However, this organism is now often assumed to be responsible for gastritis, gastric ulcers, or other gastrointestinal lesions in both young and old ferrets. Often the diagnosis is unconfirmed and response to antibiotic treatment is interpreted as confirmation of the disease. There are, however, multiple gastrointestinal disorders that show clinical improvement with antibiotic therapy (due to resolution of secondary bacterial overgrowth in the gut); response to treatment is non-specific and does not verify a specific aetiologic agent. *Helicobacter* has been claimed to cause diarrhoea with progressive wasting,[15] which are signs one would not expect even with gastric pathology; every case we have seen has had concurrent enteric disease (separate from *Helicobacter*) which was producing these clinical signs. Chronic blood loss due to severe gastric ulceration might, in severe cases, be able to produce wasting disease.

Faecal cultures, rapid urease testing of gut tissue samples, PCR (polymerase chain reaction) testing of faeces or biopsy samples, urea breath testing, stool antigen testing, and serum antibody testing can all identify a *Helicobacter* carrier.[16] However, as most ferrets are thought to be carriers, such testing is probably not useful, unless as an assessment of post-treatment eradication of the bacteria. Gastric (and intestinal) histopathology is needed to confirm a causal relationship between infection and the presence of gut lesions. Visualization of the bacteria is maximized using a silver stain (Warthin–Starry stain).

The difficulties inherent in applying laboratory research models to everyday clinical cases are numerous. The original studies promoting *Helicobacter* as a ferret pathogen involved small numbers of animals and lacked histopathologic examination of the gut, other than the stomach and proximal 1–2 cm of the duodenum where *Helicobacter* could be expected to colonize.[10,11,12] Concurrent enteritis or generalized gastroenteritis would not have been detected. Some studies utilized ferrets from a large breeder facility known to have coronavirus enteritis in its ferret population[12,17]; this virus causes lymphoplasmacytic inflammation of the ferret gut.[18] Whether concurrent coronavirus infection would influence histopathologic findings in those *Helicobacter* studies is unknown. In a study utilizing combination drug therapy to eliminate ferret *Helicobacter* infection,[17] bacterial eradication was proven successful, but the level of gastritis did not improve in five out of six ferrets. This is in contrast to human research with *Helicobacter pylori* which demonstrated that bacterial elimination produced resolution of gastritis.[19] Such results should make us question whether *Helicobacter* was the only inciting agent of the gastritis in those research cases. Perhaps a *Helicobacter*-induced gastritis might persist awhile after bacterial elimination, as can sometimes occur with humans; or perhaps other factors were inciting the inflammatory response. Some reports state that *Helicobacter* infection in ferrets is associated with chronic gastritis that increases in severity over time.[14] Whether this occurs in non-stressed house ferrets in normal clinical situations is less certain. Review of another study suggests only mild pathology induced by experimental infection: all four ferrets had *Helicobacter* colonization of the gastric fundus and antrum, but the fundal mucosa showed negligible changes, and the antral mucosa showed only mild inflammation in three ferrets (the fourth remaining normal). The severity of the lesions did not increase during the 6-month interval of the study.[10]

Helicobacter has been shown to occasionally incite development of lymphoma in the gastric mucosa (in the mucosa associated lymphatic tissue, i.e. 'MALT' lymphoma).[13] It should be noted that other forms of gastroenteritis can commonly lead to lymphoma, occasionally in the gastroenteric mucosa, but more often in the mesenteric lymph nodes associated with the gut;[8] see Inflammatory bowel disease.

Histopathologic examination of hundreds of ferret gastrointestinal biopsies has shown that in the author's pet ferret patients, *Helicobacter* does not appear to be the primary aetiologic agent for most gastroenteric lesions observed.[4,8] On pyloric-region gastric biopsy and histopathology (with silver staining) we can find the bacteria in less than 50% of ferrets with confirmed gastritis; only a small percentage of these have heavy numbers of

bacteria present. In most cases, the bacteria seem to be an incidental finding or at most a partial contributor to the inflammatory lesions. When the stomach is biopsied 2–3 cm proximal to the pylorus, we find *Helicobacter* only about 4% of the time, with only about 2% of cases having a large number of bacteria present – yet biopsies taken in this region reveal significant gastritis also. This is in contrast to the claims made in the original research studies of *Helicobacter mustelae*, wherein the researchers proposed a causal link between the bacteria and inflammatory lesions due to visualizing a close geographic association of the bacteria to the observed lesions.[11,12]

In the author's experience, most ferrets with gastritis also have enteritis which equals or exceeds the gastric lesions in severity. In a recent sampling of 115 recent gut biopsy cases, only 34 cases (29.5%) had pyloric gastritis which was more severe than the enteritis; of these, only 22 (19%) had detectable *Helicobacter* on pyloric area biopsy. By contrast, 81 cases (70%) had enteritis which equalled or exceeded the gastritis in severity – in 53 cases (46%) the enteritis was much more severe than the gastritis on biopsy. *Helicobacter* should not produce these enteric lesions; in hundreds of enteric biopsy samples (silver-stained), we have never detected *Helicobacter*-like organisms in mid-duodenal or jejunal biopsies, nearly all with enteritis present. Detection of *Helicobacter*-like organisms in intestinal fluid contents or the bowel lumen is to be expected; the organism must pass through the gut and out of the body if it is to infect additional hosts. But no causal link between this bacterium and active enteritis can be concluded, when the organism cannot be detected in any biopsies of intestinal mucosa.

One study noted antigastric autoantibodies in ferrets infected with *Helicobacter*; this might explain persistence of gastritis after bacterial eradication.[20] However, those antibodies reacted with parietal cells from the gastric mucosa, but not with duodenal or colonic mucosa, so even an immune-mediated response triggered by *Helicobacter* would not appear likely to induce enteritis. In conclusion, most ferrets with gastric disease have a more generalized gastroenteritis, with *Helicobacter* present either incidentally or as a partial contributor to the gastric lesions. Only a small percent of cases (1.7%) showed heavy *Helicobacter* growth in the gastric mucosa with a significant gastritis and minimal enteritis; these cases may be examples of primary *Helicobacter* gastritis. Based on these data, it is evident that although the bacteria may be pathogenic in certain situations, *Helicobacter*-induced pathology is probably far less common in the ferret than is currently assumed, and the bacteria are blamed for many lesions which in reality are being induced by unrelated pathology.

Signs of *Helicobacter* gastritis would include nausea, anorexia, vomiting, melaena, or bruxism; these signs all are typical of gastritis. *Helicobacter* would *not* be expected to directly produce signs of enteritis such as chronic diarrhoea without melaena, mucoid stools, greenish stools, or weight loss despite good appetite (unless from chronic vomition, or chronic heavy blood loss). Diagnosis ideally should be confirmed with surgical biopsy (not endoscopy); this allows for histopathologic sampling both of the pyloric stomach and small bowel, as well as mesenteric lymph nodes (to assess for cellular or architectural atypia and risk of lymphoma development). (See Inflammatory bowel disease discussion regarding lymph node histopathology.) If gastritis with *Helicobacter* in the lesions is confirmed via biopsy, or if the clinician elects presumptive treatment to eliminate possible infection, then several treatment protocols are available. In the past, metronidazole at 20 mg/kg p.o. b.i.d./t.i.d. plus amoxicillin at 10 mg/kg p.o. b.i.d./t.i.d. for 14 days or longer was said to eliminate infection.[14] More recent protocols have increased dosing, frequency and duration of therapy due to apparent antibiotic resistance developing.[13] Addition of bismuth subsalicylate (Pepto-Bismol) 0.5 cc p.o. b.i.d. may enhance treatment effectiveness, as bismuth compounds may aid bacterial elimination.[17] One may add acid blockers such as ranitidine (Zantac) at 3.5 mg/kg p.o. b.i.d., or famotidine (Pepcid) at 0.25–0.5 mg/kg p.o. s.i.d., or possibly omeprazole (Prilosec) at 0.7 mg/kg p.o. s.i.d. Human studies have demonstrated that acid blockers can enhance bacterial elimination.[21,22,23]

Metronidazole and bismuth subsalicylate are both distasteful to ferrets. Omeprazole is supplied as capsules containing numerous slow release granules, so is more difficult to dose in small patients; in our initial use with higher doses of this drug (4 mg/kg p.o. s.i.d.) some patients exhibited malaise and anorexia not seen with other acid blocking drugs. *Note*: when dosing this drug, one must open the capsule and count out individual granules to achieve an accurate dose.

Another protocol uses clarithromycin at 25 mg/kg p.o. b.i.d. for 14 days, combined with ranitidine bismuth citrate (not available in the USA).[17] Alternatively, clarithromycin may be combined with amoxicillin (10–40 mg/kg p.o. b.i.d./t.i.d.) and ranitidine (3.5 mg/kg p.o. b.i.d.) for 14–28 days. Pepto-Bismol can be added to this combination. A recent published human protocol used clarithromycin plus amoxicillin plus omeprazole (at human doses) and showed elimination of infection.[21] Drug resistance can easily develop with all these protocols; some human protocols now use metronidazole in place of clarithromycin due to antibiotic resistance.[22,23] One human study showed that concurrent use of sucralfate with combination antibiotic therapy enhanced efficacy similar to using proton pump inhibitors; the sucralfate bound the antibiotics and the bacteria at the mucosal surface, enhancing bacterial clearance.[24] The author's

current preference is to use drug combinations that are palatable, increasing owner and pet compliance; a fairly palatable combination is clarithromycin, amoxicillin, sucralfate and ranitidine; the first three are given together, and the ranitidine is given at least 1 hour apart to allow proper absorption from the gut without binding to the sucralfate. Famotidine would be a good alternative to ranitidine.

We have noted occasional persistence of *Helicobacter* in the ferret gut when using the above treatment protocols. This could be due to drug resistance or inconsistent drug administration, but also may be related to re-infection from the pet's own faeces or from other ferrets in contact with the treated patient. Ideally, all contact ferrets should be treated for *Helicobacter* simultaneously to maximize potential for total elimination of the organism. Their cage environment and litter boxes should be disinfected regularly during the treatment course.

If gastric ulcers are suspected due to presence of melaena, bruxism, or severe nausea, then sucralfate (Carafate) suspension may be used at 100–125 mg per ferret p.o. b.i.d./t.i.d. until signs resolve.

Inflammatory bowel disease (lymphoplasmacytic gastroenteritis)

This is an idiopathic chronic inflammation of the gastrointestinal tract, usually involving both stomach and small bowel (duodenum and jejunum). The ileum and colon are likely involved in many cases as well, based on clinical signs of colitis and proctitis; however, these sites are usually not sampled histopathologically except on necropsy. It is usually seen in ferrets over 1 year old; most commonly over 2 years old. This is one of the most common significant disease syndromes in pet ferrets today (in the USA), certainly as common as adrenal tumours or insulinomas. It is also the most underdiagnosed disease in ferrets, being virtually unrecognized until fairly recently.[8]

The inflammation of the gut mucosa and lamina propria is primarily lymphoplasmacytic, especially in the stomach, but often has a lesser eosinophilic component (mostly in the bowel). Of 115 recent intestinal biopsy cases, 35 cases (30.4%) demonstrated lymphoplasmacytic enteritis; 77 cases (66.9%) had both lymphoplasmacytic and eosinophilic infiltrates; 3 cases (2.6%) had purely eosinophilic enteritis. Of 120 recent gastric biopsy cases, 106 (88.3%) demonstrated lymphoplasmacytic gastritis; 14 cases (11.7%) had both lymphoplasmacytic and eosinophilic infiltrates; no cases had a purely eosinophilic gastritis.

Inflammatory bowel disease (IBD) cases with an eosinophilic component to the gut inflammation must be distinguished from a less common disease, eosinophilic granulomatous disease (also called eosinophilic gastroenteritis – a bit of a misnomer). This is a multiorgan disease involving eosinophilic infiltrates and granulomas of lymphatics and multiple tissues; it does involve the gut as well, but the condition is not a gut mucosa-oriented inflammatory disease and therefore is not a form of true 'inflammatory bowel disease'. In our IBD cases, the inflammatory response primarily involves the gut mucosa and lamina propria.

Possible inciting factors for inflammatory bowel disease could include food hypersensitivity, carbohydrate overload, bacterial overgrowth, gastric foreign bodies, bacterial or viral infection, toxins, aberrant immune response, etc. *Helicobacter* infection can sometimes produce a lymphocytic gastritis; coronavirus infection produces a lymphocytic enteritis. Prolonged or extravagant immune response to these infectious agents might result in chronic gastritis or enteritis that persists even when the inciting organism is eliminated.

IBD is often non-symptomatic until very advanced. Signs may be subtle, and may include a lack of proper musculature (protein malabsorption), weight loss, sporadic diarrhoea, melaena (with gastritis), bruxism due to nausea, or vomiting. Signs may be mild and chronic, or acute and severe. Acute diarrhoea (often greenish) and malaise may occur with secondary bacterial overgrowth/bacterial enteritis. Acute melaena, nausea and anorexia may occur with gastric ulceration. Acute suppurative hepatitis may be seen, producing fever, leukocytosis, occasionally icterus, and severe malaise. Figure 9.3 shows a typical IBD stool, with a mixture of greenish stool (likely due to bacterial overgrowth) and melaena (due to gastric or duodenal ulceration).

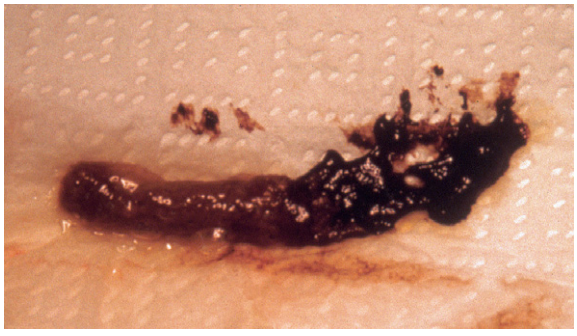

Figure 9.3 Stool from a patient with inflammatory bowel disease. The sample demonstrates green mucoid characteristics in one portion, typical of bacterial enteritis/bacterial overgrowth. The other portion of the stool demonstrates melaena suggestive of gastric or intestinal ulceration.

Often IBD is detected when patients are presented for concurrent disease (e.g. adrenal or islet cell tumours), and a thorough history, physical exam and blood profile show evidence of gut disease.

Preliminary diagnosis (i.e. high index of suspicion) can usually be made via a comprehensive blood profile and clinical signs (if present). Essential tests for evaluating gut disease include a complete blood count (CBC) test, plus serum lipase, globulin, alanine aminotransferase (ALT), and gamma-glutamyltranspeptidase (GGT). Other recommended tests in any comprehensive ferret profile include glucose, blood urea nitrogen (BUN) and creatinine kinase (CK), amylase, bilirubin, albumin, calcium, phosphorous, aspartate transaminase (AST) and alkaline phosphatase.

At our practice, comparison of serum chemistry values with gut histopathology on hundreds of cases has revealed some correlations. Elevation of lipase over 500 IU/L at commercial US veterinary laboratories,[5,6] or over 1000 IU/L using an in house IDEXX VetTest® machine[7] is consistent with gastritis or gastroenteritis in ferrets. In the author's experience, clinical pancreatitis is rare in ferrets, and produces serum elevations of both amylase and lipase. Gastric lipase seems to be the main component of most serum lipase elevations in ferrets, and amylase remains low (<100 IU/L).[8] Serum lipase elevations of gastroenteric origin have been documented in dogs and cats.[25,26,27,28]

Elevated serum globulin levels suggest inflammatory response; most confirmed IBD cases have high serum globulin levels, between 3.0 and 5.5 g/dL.[8] Serum globulins higher than 6.0 g/dL can be seen with very severe IBD, but Aleutian disease virus must be considered as a differential diagnosis whenever serum globulins approach 6.0 g/dL or above. ALT and GGT may be elevated due to secondary lymphocytic hepatitis or less commonly suppurative hepatitis (see Hepatic diseases). CBC findings are variable. A leukocytosis may be present, with a relative or absolute lymphocytosis. In other cases, a neutrophilia may be seen, suggestive of secondary bacterial infection in the gut or liver. Because chronic gastroenteritis is common, insidious and potentially fatal, annual comprehensive CBC and chemistry profiles should be recommended on all ferrets over 3 years old.

If many cases are subclinical or have only subtle signs, why diagnose and treat IBD aggressively? Because sequelae may be severe and fatal, even though the patient tolerates the underlying gastroenteritis for months or years. Sequelae include:

1. Chronic stomach or intestinal damage leads to fibrosis, bleeding ulcers, spontaneous gastric or intestinal rupture, intestinal villous atrophy and malabsorption, and/or progressive weight loss.
2. Secondary bacterial overgrowth or enteritis can produce severe illness including diarrhoea, vomition, anorexia, weight loss and sepsis.
3. Altered gastric motility may predispose to gastric acid reflux and oesophagitis, leading eventually to megaoesophagus.[4] Gastric motility alterations may also predispose to trichobezoar formation, although this connection is less easy to demonstrate.
4. Chronic malabsorption and protein deficiency can lead to muscle wasting. In theory, the cardiac muscle may be affected as well as skeletal muscles, with multiple amino acid deficiencies possibly leading to cardiomyopathy.
5. Lymphocytic enteritis can lead to ascending portal lymphocytic hepatitis; occasionally this leads to secondary bacterial infection and suppurative hepatitis.[8] Occasionally, chronic hepatitis may end in cirrhosis.
6. The most severe sequel to chronic gastroenteritis is lymphoma; this arises typically in the mesenteric nodes which have become severely hyperplastic in response to chronic gut inflammation.[8] Less often lymphoma can arise in the mucosa of the stomach or bowel. In the author's experience, undiagnosed chronic gastroenteritis is the most common trigger for lymphoma development in the pet ferret, in particular lymphomas arising in the mesenteric nodes (Ch. 13). Chronic gastroenteritis has been linked to increased risk of lymphoma development in other species as well.[29,30,31,32]

Figure 9.4 is a schematic of lesions, which may occur in various organ systems as sequelae to chronic gastroenteritis. The sequential events in the various pathways lead to end-result lesions which may be detected clinically; these lesions are shown in darker highlighted boxes. Those with question marks have a hypothesized causal association with gastroenteritis but have not been conclusively linked at this time.

Confirmation of diagnosis of IBD should be ideally done via histopathology. Gut biopsies should be obtained of the pyloric stomach, mid-duodenum, and mid-jejunum. The pyloric area biopsy should be just proximal to the pylorus itself, toward the lesser curvature of the stomach. Bowel biopsies should be on the antimesenteric border. Full thickness biopsies should be obtained ideally. A 5–7 mm wedge is easily taken for gastric biopsies; intestinal biopsies are typically only 2–3 mm long. A reversed scalpel blade is used to nick the antimesenteric surface of the bowel; the tissue everts with gentle digital pressure, allowing trimming of tissue off one margin with curved Metzenbaum scissors. Closures with 5-0 monofilament such as PDS or Maxon in simple interrupted pattern work well; gentle technique is impor-

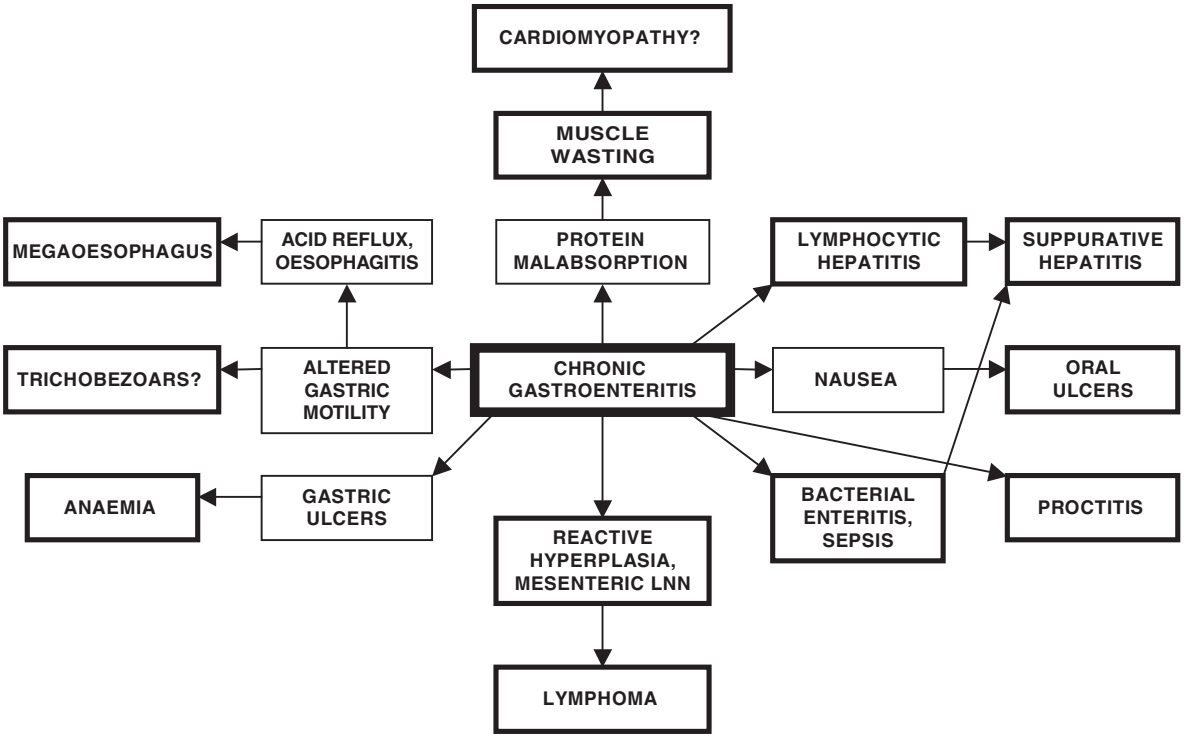

Figure 9.4 Potential sequelae to chronic gastroenteritis. Diseases with question marks (?) have a hypothesized causative association with gastroenteritis but have not been conclusively linked at this time. LNN, lymph node neoplasm.

tant to minimize tissue tearing with the small gauge suture. Gastric closure can be two layer (Ch. 18). Postoperative antibiotics are indicated whenever the gut is entered; e.g. enrofloxacin at 5 mg/kg p.o. b.i.d. plus amoxicillin at 10 mg/kg p.o. b.i.d. for 7 days postoperatively, or longer if the patient has evidence of bacterial disease.

Lymph node biopsies should be taken if any mesenteric nodes are visible. The most commonly enlarged and easily visualized are the gastric lymph nodes located in the fat near the lesser gastric curvature, and the duodenal (peripancreatic) node located just caudal to the pylorus. Figure 9.5 shows a grossly enlarged duodenal lymph node at the proximal end of the duodenum near the pylorus; a very large gastric lymph node is also visible in the fat near the lesser curvature of the stomach. Reactive lymph nodes in ferrets, unlike those of dogs and cats, demonstrate a gradation of pathology, which may be difficult to interpret: they may progress from mild to severe hyperplasia, then exhibit considerable cellular and/or architectural atypia, prior to transformation into lymphoma. A pathologist accustomed to interpreting canine and feline lymph node biopsies may mistakenly diagnose lymphoma in ferrets when the

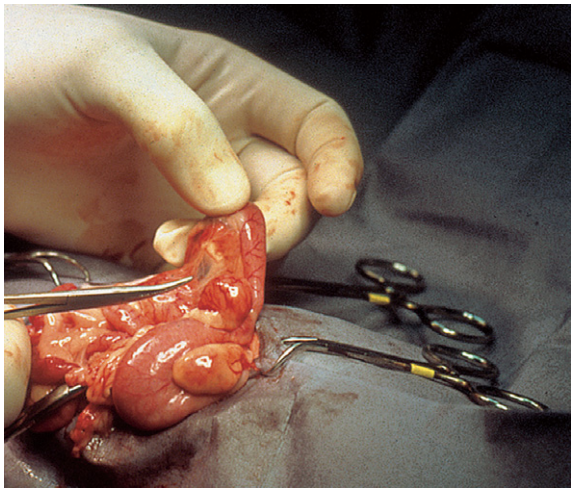

Figure 9.5 Severe enlargement of duodenal (peripancreatic) and gastric lymph nodes. The duodenum is held elevated, with forceps pointing toward the duodenal node adjacent to the pylorus. The stomach sits in the foreground, with a large gastric lymph node visible in the fat adjacent to the lesser gastric curvature.

nodes are only hyperplastic or preneoplastic. Therefore, pathologists not familiar with the histologic appearance of ferret lymph nodes should interpret nodal changes conservatively. Lymphoma should be suspected when histologic exam reveals obliteration of nodal architecture, and when gross exam of the patient reveals very large firm mesenteric or peripheral lymph nodes. Hyperplastic nodes, even when fairly large (over 1 cm diameter) are usually soft, and often oedematous; they may rupture when handled and drain serous fluid. Neoplastic nodes tend to be firm and solid even when sectioned. Ideally biopsy an entire node, as wedge biopsies may not represent the complete nodal architecture or cell population especially if the wedge sample enters a lymphoid follicle. Patients with cellular or architectural atypia in the nodes (which signify a potential for future transformation to lymphoma) warrant aggressive treatment. Figure 9.6 is a (ventral aspect) diagram of gut and lymph node biopsy sites in the ferret. If serum ALT or GGT elevations were noted, the liver should be biopsied as well; the tip of a lobe (such as the quadrate lobe) may be easily biopsied via suture ligation.

Biopsies should be read by a pathologist experienced in interpreting ferret gut histopathology. The author's samples are read by Dr Mike Garner.[a] The gut and lymph node lesions are identified, and graded as mild, moderate or severe, and any atypia is noted. Possible contributors to gut inflammation, such as *Helicobacter* or cryptosporidia are also noted when detected.

Treatment is aimed at eliminating possible underlying causes of gut inflammation and suppressing the inflammatory response. The long-term goals are suppressing the disease, thereby minimizing further tissue damage, allowing healing of gut mucosa, rebuilding the body's muscle mass, and preventing development of lymphoma. Initial therapy may include controlling existing sequelae such as gastric ulcers or bacterial overgrowth/enteritis; some patients present in poor condition and require aggressive supportive therapy prior to any surgical biopsy. Patients with signs suggestive of bacterial enteritis (diarrhoea, mucoid stools, green stools, bruxism, anorexia, thin body condition) may be treated initially with enrofloxacin at 5 mg/kg p.o. b.i.d. for 14 days plus amoxicillin at 10–20 mg/kg p.o. b.i.d. for 14 days; treatment may be extended if signs recur when medication is withdrawn. Force feeding with Hill's a/d diet, occasionally with added high calorie supplements such as Nutrical (EVSCO, USA), Ferretvite (8 in 1 Pet Products, USA) or human Ensure (Abbott Laboratories, USA), may help stabilize underweight weak patients. If gastroduodenal ulcers are suspected, they should be treated accordingly (see Gastric ulcers). Antiemetics such as metoclopramide (0.5–1.0 mg/kg p.o. or s.q. s.i.d./b.i.d.) may be useful if the patient appears nauseated when fed.

Ideally, long-term treatment should be based on gut histopathology. Treatment may begin once post-surgical healing is complete, usually 10–14 days postoperatively. If gastric biopsies reveal a significant *Helicobacter* presence coupled with lymphocytic gastritis, treatment to eliminate this organism should be initiated (see *Helicobacter* gastritis). Alternatively, as most ferrets carry *Helicobacter* in their gastric mucosa, one may decide to treat every gastritis patient presumptively, although *Helicobacter* may not be a significant contributor to gastritis in many patients. Presumptive treatment for *Helicobacter* should be performed in any patient who did not undergo gut biopsy as part of the diagnostic workup.

After *Helicobacter* treatment (if performed) is completed, long-term anti-inflammatory therapy should begin. Our drug of choice is azathioprine (Imuran); long experience with this drug in ferrets has shown it to be superior to corticosteroids in several respects. Corticosteroids used at immunosuppressive doses in ferrets will eventually produce unwanted side-effects, including loss of body condition (muscle wasting, fat deposition and 'pot belly'), hair thinning, increased risk of gastric ulceration, and hepatopathies. Patients with pre-existing hepatic pathology such as lymphocytic hepatitis or vacuolar hepatopathy (from concurrent adrenal endocrinopathy) seem particularly prone to prednisone-induced hepatopathies. These patients will sometimes demonstrate clinical malaise and severe elevation of serum hepatic enzymes (ALT, GGT) after even brief dosing with

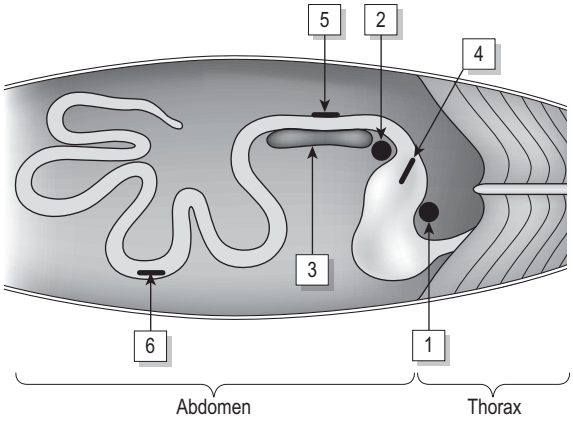

Figure 9.6 Gastrointestinal and mesenteric lymph node biopsy sites. **1.** Gastric lymph node; **2.** Duodenal lymph node; **3.** Right lobe of pancreas; **4.** Gastric biopsy site; **5.** Duodenal biopsy site; **6.** Jejunal biopsy site.

[a] Dr Mike Garner, Northwest ZooPath, Snohomish, Washington, USA. Tel: 1-360-794-0630; e-mail: zoopath@aol.com

corticosteroids. None of these sequelae are commonly seen with azathioprine, and bone marrow suppression or immune insufficiency are rare at the doses recommended. Azathioprine is easily compounded into a 5 mg/mL suspension which is pleasant tasting and stable for months. The azathioprine dosing protocol varies depending on the severity of the lesions being treated. Patients with gastroenteritis classified as mild or moderate may be placed on azathioprine dosed at 0.9 mg/kg p.o. q. 48 h. (This conservative dose regimen is also used if the patient did not undergo gut biopsy and is being treated presumptively based on history, clinical signs and CBC/serum chemistry findings.) The dosing frequency may be increased to 0.9 mg/kg p.o. s.i.d. in patients with severe or refractory clinical signs. Patients with gastroenteritis classified as severe, or who have lymphoid atypia present in gut mucosa or lymph node biopsies, should be placed on daily azathioprine dosing immediately. Cellular or architectural atypia in the nodes suggest potential for future transformation to lymphoma and always should be treated aggressively.

If prednisone is used instead of azathioprine, the dose is typically 2 mg/kg p.o. s.i.d.; concurrent use of corticosteroids with azathioprine may increase the risk of drug side effects and is not usually recommended.

Response to azathioprine is gradual, and 6 to 12 weeks may be needed for suppression of inflammation, healing of gut mucosa, resolution of clinical signs, and improvement in overall body condition. Rarely bone marrow suppression may be seen at s.i.d. dosing, usually manifesting as neutropenia. One patient demonstrated a gradual non-regenerative anaemia which improved when the azathioprine dose was reduced. Ideally perform a CBC within 3–4 weeks of starting therapy, then every 2–3 months thereafter. Patients who are stable on initial evaluations may be checked less frequently long term. Serum chemistries should be checked after 3–4 weeks on therapy, then every few months thereafter; the primary tests of concern are the serum lipase and globulin levels which may reflect the severity of the gut inflammation and hepatic enzymes (ALT and GGT), especially if hepatitis has been documented previously.

A small percentage of patients may not demonstrate adequate improvement in clinical appearance or in CBC/serum chemistry parameters on the above azathioprine doses. If no leukopenia is noted, the dose may gradually be increased to effect in these patients. Response to each dosage increase should be evaluated for 6–8 weeks prior to additional increases; re-check the CBC and serum chemistries 4–6 weeks after any dose increase to assess response and drug tolerance.

Dietary management is also recommended if the ferret will eat alternate diets. Several approaches may be taken:

1. *Allergen avoidance-hydrolyzed diets* such as Hills Z/D feline, or other strictly formulated feline select protein diets that avoid common protein sources (meats and grains), may allow reduction of gut inflammation if an underlying food hypersensitivity exists. An 8–10-week strict feeding trial is recommended. Some of our patients have shown clinical improvement (better stools, weight gain) on such diets, but whether this was due to allergen avoidance or simply better digestion of a particular formulation is uncertain. Many ferrets fail to show clinical improvement on these diets.
2. *Carbohydrate reduction*: Some carnivores are known to have trouble with chronic diarrhoea and digestive disturbances when fed dry kibble diets, whereas canned formulas produce fewer problems. The difference is thought to be the higher carbohydrate content of dry foods; starch is added to help form a more cohesive kibble. More recently, some low carbohydrate dry foods have been produced, such as Purina DM feline diet, Hills MD feline, and Pretty Pets Natural Gold diet for ferrets. These tend to have very high protein content and significantly reduced carbohydrate content, in theory ideal for ferrets. Some of our patients who fail to improve on allergen avoidance formulas have instead shown improvement on low carbohydrate formulas.
3. *Increased dietary fibre*: Some patients with chronic diarrhoea and bacterial overgrowth show clinical improvement when a high fibre formula such as Hill's W/D feline is added to the diet, either as part of a mix or as the exclusive diet. Despite the lower fat content, some patients actually gain weight due to improved gut function.

Despite dietary management, elimination of contributing factors such as *Helicobacter* or foreign bodies, and use of anti-inflammatory medications, IBD tends to be a long-term disease which remains active but suppressed with treatment. Therefore, chronic medication and monitoring are usually necessary. Resolution of clinical signs does not indicate a cure; only about half of our IBD patients had recognizable clinical signs *prior* to treatment, and were detected initially via evaluation of serum chemistries. With early detection, proper work-up and treatment, lymphocytic gastroenteritis can be controlled and severe sequelae avoided in most patients. With good control, we can minimize chronic wasting and loss of body condition, and reduce risk of mesenteric lymphoma. As a result, we see more ferrets living past the age of 8 years than ever before.

Intestinal foreign bodies

These are typically ingested pieces of soft rubbery material which ferrets are prone to chew and swallow; small trichobezoars can also occasionally leave the stomach and become lodged in the small bowel, usually the duodenum or proximal jejunum.

Signs are usually acute and severe, and may include bruxism, anorexia, vomiting, lethargy, weakness, fever or hypothermia, gastric distension and shock. If the object is slowly moving, signs may be less severe; the patient may be even be drinking or eating minimal amounts.

Careful palpation often reveals a firm movable abdominal mass effect. Radiographs often show a gas pattern in the stomach and proximal bowel with moderate distension; rarely a radio-dense foreign body such as a fruit pit may be seen; more often the object is radiolucent material such as soft rubber (Ch. 16). Barium may reveal a flow obstruction, but often does not outline the foreign body. Treatment is via enterotomy; use postoperative antibiotics for 7–14 days; enrofloxacin + amoxicillin is a good combination. Bowel resection and anastomosis is occasionally indicated if the obstructed bowel segment appears non-viable (Ch. 18).

Coccidia

No gastrointestinal parasite is very common in ferrets in the USA, but coccidiosis is occasionally seen, usually in stressed juvenile ferrets. Suspect concurrent disease with immune suppression if coccidiosis is detected in an adult ferret. Signs, when present, may include diarrhoea, tenesmus, mildly prolapsed rectal mucosa, and in severe cases, dehydration or weight loss. Diagnosis is via faecal flotation; treat with oral sulfonamides for 3 weeks. Albon (sulfadimethoxine) is effective; administer at 50 mg/kg p.o. s.i.d. on day 1, then 25 mg/kg p.o. s.i.d. for 14–20 days. Trimethoprim-sulfa is an alternate therapy, used at 30 mg/kg p.o. s.i.d./b.i.d. for 14–21 days (see Ch. 10).

Coronavirus enteritis (ECE)

This is a relatively new viral disease appearing first in the Eastern USA over a decade ago[18]; it rapidly spread across the USA, possibly as a result of large scale breeder facilities producing infected ferrets. It has been named epizootic catarrhal enteritis (ECE).

This virus is highly contagious via contact with infected ferrets, or their faeces or fomites. Coronaviruses may persist in the environment for considerable intervals (weeks or longer) under the right conditions. Disinfectants easily kill the virus.

This infection is unusual in 2 respects: (1) The younger the host is at time of infection, the fewer clinical signs are generally seen. (2) The ferret carries the virus long after clinical signs have resolved, and remains contagious to other ferrets for up to 6 months, perhaps longer.

Ferrets under 4 months old at time of infection often show no clinical signs. Ferrets 5–18 months old usually show mild to moderate signs, with severity gradually increasing with increased host age. Ferrets over 4–5 years old have the greatest risk of becoming severely ill when infected. However, the virulence of this virus appears to have been greatly reduced since the early years of viral spread across the USA. Whereas ferrets in the early 1990s often became severely ill (and many older ferrets died due to severe intestinal damage and nutrient malabsorption), death from ECE is uncommon now even in older ferrets, if adequate treatment is provided.

Onset of signs usually occurs within 48–96 h of exposure. Vomition is often seen in the first 48–72 h of illness, usually ceasing thereafter. Greenish mucoid to watery diarrhoea is the most common clinical sign, with rapid weight loss being seen in more severe cases. Milder cases may show little weight loss; diarrhoea is sometimes brown rather than green. Occasional cases may have melaena due to gastric or intestinal ulceration. Weight loss in severe cases may be extreme within the first 7–10 days of the illness even if the ferret is eating well. This is due to severe damage to enteric mucosa, with nutrient malabsorption and possibly protein-losing enteropathy contributing to the wasting disease.

Ferrets are not overly prone to hepatic lipidosis, but the rapidity of weight loss with this disease can sometimes produce significant lipidosis, especially in ferrets who were initially heavy. The gut inflammation can also predispose to ascending biliary or portal hepatitis, potentially impacting hepatic function.

No diagnostic serology is available; suspect ECE based on clinical signs of (usually) greenish diarrhoea with rapid onset, *plus* history of recent exposure to a new ferret. (This exposure could include the owner handling a baby ferret at a pet store.) The index of suspicion is higher if multiple ferrets are showing signs concurrently. Routine blood profiles may show mild lymphocytosis, as the inflammatory response in the intestine is primarily lymphoplasmacytic. However, secondary bacterial infection may induce a neutrophilia, or the leukocyte counts may be normal, so CBC changes are not diagnostic. Serum chemistry testing may reveal elevation of serum lipase or globulin due to gut inflammation (see Inflammatory bowel disease discussion), and elevated ALT or GGT if ascending lymphocytic hepatitis or hepatic lipidosis is present. Serum CK and AST tests may be elevated

if muscle damage is present due to wasting disease. Hypoalbuminaemia may be seen with severe wasting illness. A more definitive diagnosis can be made via histopathologic examination of intestinal biopsies (usually post mortem). Immunohistochemistry testing of the gut mucosa for coronavirus can be performed.

Treatment is mainly supportive. Antibiotics may reduce secondary bacterial enteritis and improve clinical signs, reducing nausea and diarrhoea. Often the stool becomes less green with antibiotic usage. Metronidazole in particular seems to improve stool color and consistency, possibly due in part to its anti-inflammatory effects – the usual dosage is 20 mg/kg p.o. b.i.d. Enrofloxacin (5 mg/kg p.o. b.i.d.) plus amoxicillin (10–20 mg/kg p.o. b.i.d.) also can produce clinical improvement and is more palatable.

Severe malabsorption cases may show progressive wasting despite aggressive feeding, and may need extensive supportive care including total parenteral nutrition (Ch. 20). However, this is a rare scenario in the past 6 years as the most virulent viral strains seem to have vanished, likely due to selective pressures favoring milder strains which allow host survival and prolonged viral shedding.

No vaccines are available. Prevention is via avoidance; owners of older ferrets should exercise caution when handling unknown ferrets, especially juveniles. There is risk when purchasing a new young ferret as a companion for an older pet, especially if the ferret came from a large scale breeder facility in the USA. When handling such animals in hospital, proper isolation and disinfection techniques should be utilized to minimize contagion to other patients.

Eosinophilic granulomatous disease ('eosinophilic gastroenteritis')

This is an uncommon disease of unknown etiology.[33,34,35] It is characterized by eosinophilic infiltrates and granulomas involving the abdominal lymphatics and multiple organs. The intestines are usually involved when cases are recognized, but the inflammatory process does not appear to originate in the gut mucosa; it is more an eosinophilic lymphangitis. Thus, this is not a form of true 'inflammatory bowel disease', and the term 'eosinophilic gastroenteritis' is misleading.

Potential aetiologies could include allergic or parasitic disease; no parasites have been shown to be linked to this syndrome. Clinical signs, when present, can include diarrhoea of variable appearance, anorexia, weight loss, vomiting or lethargy. Severe cases may exhibit grossly bright red, thickened small bowel loops, some with clear cystic structures on the serosal surfaces (lymphangiectasia). This disease can be severe and can produce more profound gross lesions than with most inflammatory bowel disease (IBD) cases (Fig. 9.7). Early cases can be subclinical as with IBD.

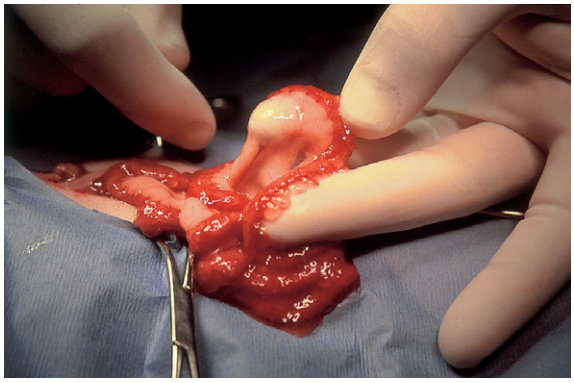

Figure 9.7 Eosinophilic granulomatous disease. In this advanced case, the intestinal loops are diffusely bright red, with clear vesicles (lymphangiectasia) present on the serosal surfaces.

Diagnosis follows the same clinical and CBC/serum chemistry parameters as with IBD; occasionally an absolute and relative eosinophilia may be seen. Gut and lymph node biopsy is needed to confirm diagnosis, and to differentiate this disease from IBD which often has an eosinophilic component. Eosinophilic granulomatous disease is uncommon and should not rate a high index of suspicion unless severe eosinophilia is present or grossly red thickened bowels are noted surgically. Intestinal lymphoma may also produce diffusely thickened red bowel segments on occasion.

Treat as with IBD; try to use a select protein diet if possible. This disease may be more difficult to manage than IBD but usually responds to anti-inflammatory treatment (azathioprine at 0.9 mg/kg p.o. s.i.d. long term).

Bacterial overgrowth/bacterial enteritis

Bacterial overgrowth and/or enteritis appear to be common in ferrets, usually secondary to underlying gut pathology such as inflammatory bowel disease or coronavirus enteritis. Other possible inciting factors could include dietary indiscretion, diet changes, coccidiosis, intestinal neoplasia, debility and foreign body ingestion.

Signs usually include diarrhoea (often greenish); more severe cases may demonstrate bruxism, anorexia, weight loss and occasionally vomition. Signs may be mild and sporadic; episodes are typically acute but may be weeks or months apart. Repeated episodes (if unrelated to diet changes or dietary indiscretion) strongly suggest underlying gut pathology.

Treat with broad spectrum antibiotics; enrofloxacin 5 mg/kg p.o. b.i.d. + amoxicillin 10–20 mg/kg p.o. b.i.d.

for 10–14 days usually works well. Metronidazole may also be used at 20 mg/kg p.o. b.i.d.

Enterotoxaemia

Bacterial enterotoxaemia is an uncommon but potentially deadly sequel to severe gastrointestinal disease and disruption of normal gut flora, such as can occur with inflammatory bowel disease, bacterial overgrowth, coronavirus enteritis, etc. Weak debilitated animals may be more prone, but incidence of enterotoxaemia is always low. The responsible organism is probably a *Clostridium* species.

Signs include diarrhoea, depression, hypothermia, shock and death. Enterotoxaemia may be suspected in a patient who has gastrointestinal disease and initially seems stable, then suddenly destabilizes, is very weak and is hypothermic. Differential diagnoses could include septicaemia, or septic peritonitis due to a perforated ulcer, or acute heavy gut bleeding due to ulceration, etc.

Treatment must be rapid and aggressive. Give broad spectrum antibiotic therapy which targets anaerobic infections well (such as metronidazole 20 mg/kg b.i.d. and amoxicillin 10–20 mg/kg b.i.d.). Toxin binding agents such as activated charcoal may be of benefit. Warmed i.v. fluids and supportive care are indicated (Ch. 20).

Mortality may be high with enterotoxaemia. Prevention is the better approach to this problem; use broad spectrum antibiotics such as enrofloxacin plus amoxicillin with any patient demonstrating significant signs of GI disease. Initiate supportive care if progressive weight loss is noted, before the patient is debilitated. Necropsy reveals large areas of small bowel which are dark red to black in color; otherwise findings are unremarkable (Fig. 9.8).

Aleutian disease virus

This is a chronic parvoviral disease of ferrets which may be subclinical or may on occasion produce clinical signs and hypergammaglobulinaemia. The virus can damage multiple organ systems, including kidneys, eyes, lungs and brain.[4] (See also discussion in Ch. 8.) This disease is mentioned here because wasting disease and diarrhoea with melaena have been reported in severe cases.[36] In the author's experience, ferrets with significant clinical Aleutian disease usually demonstrate an elevation in total serum globulin, occasionally as high as 14.0 g/dL. Other causes of chronic inflammation such as inflammatory bowel disease may also elevate serum globulin levels. However, total serum globulin levels in excess of 6.0 g/dL tend to be highly suspicious for Aleutian disease viral infection, as other inflammatory diseases usually produce lesser elevations.[8] Aleutian disease virus should be suspected when high serum globulin levels and chronic wasting disease or malaise are noted. Renal disease, mild respiratory distress due to viral pneumonia, ocular lesions such as uveitis, or CNS signs may also be present with this disease. Until recently, serologic confirmation of viral infection was available using counterimmunoelectrophoresis (United Vaccine Lab, USA). This laboratory no longer offers Aleutian virus testing, but the test is now available through the Blue Cross Animal Hospital, which has obtained United Vaccine Lab's reagents. (Serum samples should be addressed to Blue Cross Animal Hospital, c/o Dr Blau/CEP testing, 401 North Miller Avenue, Burley, Idaho, USA 83318.) Although serology can detect a viral carrier, causal linking of viral infection to gut lesions would require histopathology. Histologic findings would typically be a primarily plasmacytic inflammatory infiltrate in the gut tissues.[4] Treatment is primarily supportive care and anti-inflammatory medication; azathioprine dosed at 0.9 mg/kg p.o. s.i.d. has reduced serum globulin levels and reduced severity of signs in some of the author's patients. Broad spectrum antibiotics such as enrofloxacin 5 mg/kg p.o. b.i.d. plus amoxicillin 10 mg/kg p.o. b.i.d. may reduce severity of diarrhoea and malaise by reducing secondary bacterial overgrowth or enteritis. This is an uncommon primary cause of gastrointestinal disease in the ferret in the author's experience, and should have a low index of suspicion when evaluating most ferrets with gastrointestinal signs.

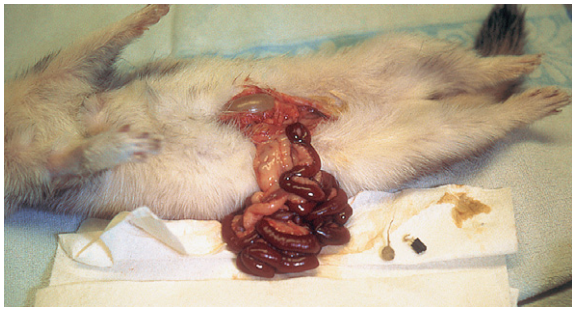

Figure 9.8 Enterotoxaemia. The affected bowel loops are dark red to black, typical of Clostridial enterotoxaemia. This necropsy was performed immediately post mortem.

Neoplasia

Lymphoma is the most common gastrointestinal neoplasm encountered, likely due in many cases to chronic unrecognized inflammatory disease of the gut, such as caused by inflammatory bowel disease, *Helicobacter* gastritis, food hypersensitivity, or other factors. Lymphoma often appears to arise in the mesenteric lymph nodes first, but also can arise in the gut mucosa, or metastasize there from other locations. Signs vary depending on the location and extent of the lesions (Ch. 13). Often gradual weight loss and/or palpable abdominal masses are noted. Discrete masses involving the gut can lead to

bowel obstruction. Intestinal lymphoma can also cause diffusely thickened red bowels that resemble those seen with eosinophilic granulomatous disease. The red thickened lesions can be localized to small segments of bowel or involve the entire gut from duodenum to rectum. Diffuse infiltration of the bowel or stomach wall can lead to spontaneous perforation of the gut and septic peritonitis. The CBC may be unremarkable; lymphocytic leukaemia occurs only in a small percentage of cases. Serum chemistry tests may reveal elevated lipase and globulins suggestive of chronic gut inflammation; CK may be elevated with weight loss and muscle wasting. ALT may be elevated if neoplasia involves the liver.

Treatment of lymphomas is via chemotherapy; protocols vary from simple and inexpensive (e.g. prednisone alone), to moderately aggressive and moderately effective (e.g. Tufts University protocol), to the most aggressive and probably most effective (e.g. University of Wisconsin protocol). Response to treatment may be more rewarding with high grade lymphomas (Ch. 13).

Other neoplasia involving the gut is occasionally seen, such as pancreatic (exocrine) adenocarcinoma or primary bowel cancer. Signs vary depending on the location and extent of lesions, as with lymphoma. Prognosis for cure is poor with most of these neoplasms unless the lesion is localized and resectable (Ch. 13).

Proliferative bowel disease (proliferative ileitis)

This rather rare condition is caused by an intracellular bacterium, *Lawsonia intracellularis*.[37] The disease is characterized by inflammation and thickening of the ileum and/or colon (which often become palpable) and by diarrhoea of variable appearance and severe wasting. Unlike coronavirus, this disease affects mostly young ferrets younger than 1.5 years old, and does not respond to supportive care alone. Also, this disease targets the lower bowel, and can produce severe tenesmus and rectal prolapse.

Treatment is with chloramphenicol at 50 mg/kg p.o. b.i.d. for at least 2 weeks, longer in severe or chronic cases. Other antibiotics appear to be less effective.[37]

This illness appears to be rare, at least in the Western USA, and the author has not seen a confirmed case in nearly 20 years of clinical practice involving ferrets. The author's pathologist Dr Mike Garner (see p. 212) reads histopathology samples from across the USA and has only seen one case of this disease. Most enteric disease (with diarrhoea) which the author sees in ferrets responds clinically to amoxicillin combined with enrofloxacin or metronidazole, plus addressing any underlying gut disease. Thus proliferative bowel disease should have a very low index of suspicion, unless a palpably firm thickened lower bowel segment is noted or severe rectal prolapse is seen. Even with those clinical findings, intestinal lymphoma would be a more likely diagnosis than proliferative bowel disease in the author's experience.

Proctitis

This condition is occasionally seen, and appears as a grossly red, swollen and sometimes protruding anus. Severe cases may appear to have rectal mucosa prolapsing moderately. Tenesmus and pain on defecation are often noted.

Proctitis is seen most commonly concurrent with other gut pathology, such as inflammatory bowel disease, bacterial enteritis, or other disease that produces chronic diarrhoea or colitis. In these cases, proctitis could result from soiling and irritation of anal tissues due to chronic diarrhoea, or could represent a direct extension of an inflammatory process involving the rectal mucosa.

Initial treatment involves topical anti-inflammatory medication; one of the more effective is Anusol-HC (human haemorrhoid cream with hydrocortisone). Alternatively, an antibiotic + cortisone combination cream may be useful. Some cases respond better when oral enrofloxacin is used concurrently, suggesting a bacterial component to the proctitis. This condition may recur; long-term management should include evaluation for (and treatment of) any other gastrointestinal pathology present.

In rare cases of true rectal prolapse, the tissue should be replaced in situ and a 3-0 nylon purse string suture applied to prevent recurrence of the prolapse; the suture should be maintained for 14–21 days minimum provided that the patient tolerates the sutures well and can defecate normally.

Hepatic diseases

Hepatic pathology is common in ferrets and is often subclinical. The most common diseases encountered are hepatitis (usually ascending portal inflammation secondary to gastroenteritis), vacuolar hepatopathy (secondary to adrenal hormonal dyscrasias or cortisone administration), or a combination of both of these processes. Less commonly, neoplasia or other pathology may be seen. Serum chemistry evaluation is a useful tool in detecting hepatic pathology and in monitoring response to treatment. Histopathology is often required for definitive diagnosis and grading of lesions.

Lymphocytic hepatitis

This is very common in pet ferrets and is often unrecognized as it is usually subclinical. Lymphocytic hepatitis usually occurs secondary to gut disease, e.g. inflammatory bowel disease or other causes of chronic gut inflammation such as coronavirus.[8] A published report identified spirilliform bacteria resembling *Helicobacter* in hepatic biopsies of several ferrets with cholangiohepatitis,[38] but none of our cases have yielded similar findings.

The inflammation is typically a lymphocytic portal hepatitis, suggesting an ascending inflammatory process from the gut. Biliary inflammation is often noted.

Most cases are diagnosed incidentally when a blood profile is run; most patients are over 1.5 years old when diagnosed. Signs, if present, may include lethargy, anorexia, weight loss, bruxism, diarrhoea or vomition. Many of these signs could be due to gut disease which is often present. Preliminary diagnosis (i.e. high index of suspicion) is made via serum chemistry analysis. Lymphocytic hepatitis usually produces moderately elevated serum ALT (200–500 IU/L) and often GGT. Concurrent vacuolar hepatopathy from adrenal endocrinopathies may elevate the ALT further. Concurrent gut inflammation may produce elevated serum lipase and/or globulin levels. Most cases of lymphocytic hepatitis do not show elevation of serum AST, alkaline phosphatase or bilirubin. These are insensitive tests for hepatic disease in ferrets and typically elevate only with severe hepatic lesions such as suppurative hepatitis or neoplasia. AST is also a non-specific test and elevates readily with muscle damage, including wasting due to severe weight loss. Check for elevated CK if the serum AST exceeds the ALT, because even with severe liver disease ALT always elevates faster and more dramatically.

Interpreting serum chemistries:

- *ALT* = 200–700 IU/L: Mild to severe lymphocytic hepatitis, or mild to moderate suppurative hepatitis, or vacuolar hepatopathy, or occasionally lipidosis
- *ALT* = over 1000 IU/L: Severe suppurative hepatitis, or neoplasia
- *GGT* = over 10 IU/L: Ascending biliary inflammation and/or stasis suggested
- *AST* elevation only is seen in severe hepatic disease or muscle wasting
- Alkaline phosphatase elevation suggests severe biliary pathology and/or obstruction, such as with severe suppurative hepatitis or neoplasia
- Bilirubin elevation (over 0.9 mg/dL) suggests severe suppurative or neoplastic hepatic disease, or haemolysis. However, ferrets clear bilirubin very efficiently via the kidneys; urinalysis often reveals bilirubinuria with normal serum bilirubin concentrations.

Confirmation of diagnosis is via liver biopsy, ideally via laparotomy. Ultrasound-guided biopsy may be performed; avoid needle aspirates as they often are not diagnostic (Ch. 17). Most cases warrant gut biopsies as hepatitis in ferrets usually is secondary to chronic gastroenteritis; include the mesenteric lymph nodes (see Inflammatory bowel disease). Suture ligature of a lobe tip is an easy biopsy technique, if no focal hepatic lesions are noted.

Treatment is similar to that for inflammatory bowel disease. Azathioprine dosed at 0.9 mg/kg every 1–2 days p.o. is recommended long term; monitor progress via evaluation of serum ALT and GGT regularly (and lipase/globulin, if these are elevated due to gastroenteritis). Also evaluate the CBC 4 weeks after initiating therapy, then every 3–4 months thereafter while using azathioprine. Human studies have shown that azathioprine combined with low dose prednisone controlled inflammation as well as high dose prednisone alone. Some anecdotal reports in canine chronic active hepatitis indicated improved results when azathioprine was used with prednisone, as opposed to prednisone alone.[39] In ferrets, prednisone can exacerbate hepatic pathology in some cases and is not recommended. Some ferrets with pre-existing hepatopathies may demonstrate severe elevations in serum ALT levels soon after prednisone dosing begins, often with profound clinical malaise.[4]

Cases with severe or refractory elevations of ALT or GGT may benefit from addition of ursodiol (Actigall) at 15 mg/kg p.o. s.i.d. to reduce biliary stasis via thinning of biliary secretions; it also has anti-inflammatory effects. S-adenosylmethionine (SAMe) may be of benefit in some cases also – it reportedly has antioxidant and cell membrane-protective properties. The typical dose is 20 mg/kg per day for dogs; we have not evaluated its use in ferrets at this time. Silymarin (milk thistle) is a flavinolignan mixture with purported antioxidant properties. Its efficacy in treating liver disease in humans, dogs, cats and ferrets has not been demonstrated adequately.

Control of ferret hepatitis usually requires recognition and control of any concurrent gut pathology such as inflammatory bowel disease; control of gastroenteritis often resolves the hepatitis. Untreated lymphocytic hepatitis may lead to episodes of acute suppurative cholangiohepatitis, cirrhosis or possibly neoplasia.[4,40]

Suppurative hepatitis

This form of hepatitis is far less common than lymphocytic hepatitis, but is more recognizable due to its often profound clinical signs. Mild cases may be subclinical, but severe cases can be acute and dramatic. There is

probably underlying lymphocytic gastroenteritis present in most cases, leading to intestinal bacterial overgrowth, ascending biliary inflammation, and lymphocytic hepatitis, all of which predispose the patient to bacterial cholangiohepatitis. In a few cases, liver biopsies reveal neutrophilic infiltration patterns suggestive of blood-borne sepsis, but most are portal hepatitis typical of ascending disease from the GI tract.[4]

Acute severe cholangiohepatitis produces significant clinical signs: lethargy, anorexia, fever, vomition or diarrhoea may all occur, as well as icterus. Normal ferrets may have a slight yellowish cast to the skin due to sebaceous secretions, and icterus may be subtle and overlooked. The nose, ears and oral cavity are good locations for visualizing icterus, as is the serum (Fig. 9.9). Urine may be vivid deep yellow or greenish tinged with bilirubinuria.

Subclinical cases are discovered via serum chemistry analysis; usually serum ALT and GGT are the best indicators of ferret hepatopathy and are likely to elevate even with milder cases (see lymphocytic hepatitis for discussion of serum chemistry evaluation). Severe cases may demonstrate ALT levels well over 1000 IU/L, with lesser elevations of GGT, AST and even alkaline phosphatase. Serum bilirubin may be elevated. Ferrets clear bilirubin efficiently via the kidneys, which may lead to bilirubinuria with fairly normal serum bilirubin levels. The CBC may reveal leukocytosis with neutrophilia in some cases.

Definitive diagnosis is via histopathology; in milder cases, this is the only way to differentiate this condition from the more common lymphocytic hepatitis. Severe cases with large chemistry elevations should create immediate suspicion of suppurative disease, and broad spectrum antibiotic therapy should begin. An effective combination is enrofloxacin at 5–10 mg/kg p.o. b.i.d. + amoxicillin at 10–20 mg/kg p.o. b.i.d. for at least 14 days. Supportive care (fluids, force feeding, control of diarrhoea or nausea, etc.) should be given as needed. Serum chemistries and clinical appearance often improve dramatically within 3–5 days, and the patient may appear clinically normal at the end of therapy. Serum chemistries should be evaluated after 14 days even if recovery appears complete. Mild persistent ALT or GGT elevations suggest underlying pathology such as lymphocytic hepatitis; elevated serum lipase and/or globulin levels may also suggest underlying gut pathology such as inflammatory bowel disease. Suppurative hepatitis is usually secondary to another disease process; this should be investigated and addressed in order for long-term management of the patient to be successful (i.e. hepatic and gastrointestinal biopsies may be indicated).

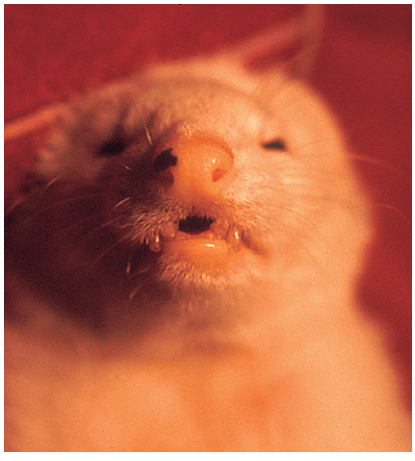

Figure 9.9 Icterus in a ferret with suppurative hepatitis. *Note* the yellow nose and lips. Icterus is often subtle and overlooked in ferrets.

Vacuolar hepatopathy

This is a histopathologic diagnosis, wherein increased vacuolization of hepatocytes is observed. The typical cause is endocrinopathy, such as caused by adrenal tumours with elevation of sex hormones such as estradiol. Corticosteroid administration may also produce this condition.

Most cases are subclinical, but might be suspected when mild to moderate persistent serum elevations of ALT (and sometimes GGT) are seen in a patient with adrenal disease. The main differential diagnosis is lymphocytic hepatitis; only hepatic biopsy can differentiate the two conditions. Clinical signs tend to be mild and non-specific, e.g. malaise, mild anorexia, or lethargy.

This condition usually produces minimal to mild ALT elevations (200–350 IU/L). However, cases with concurrent lymphocytic hepatitis and vacuolar hepatopathy may demonstrate persistent serum ALT levels as high as 400–550 IU/L, with minimal clinical signs and no apparent progression of disease for long periods.

Treatment includes elimination of underlying causes, i.e. adrenal disease or prednisone administration. Other therapies when clinical signs are present may include ursodiol (Actigall) at 15 mg/kg p.o. s.i.d., anti-nausea medications and general supportive care.

Hepatic lipidosis

Ferrets are not overly prone to severe lipidosis, but certain situations may predispose a patient to this disease. The most common would be a heavy older ferret who loses weight suddenly, such as from infection with corona-

virus enteritis. Other hepatic disease such as lymphocytic hepatitis may compromise hepatic function and predispose to lipidosis in the face of weight loss. Steroid usage, endocrine dyscrasias and other factors may also influence the incidence of this disease.

The clinical presentation is variable. Many cases of lipidosis are subclinical, and presenting signs are often related to whatever disease process precipitated the initial weight loss (e.g. coronavirus enteritis, suppurative hepatitis, neoplasia, sepsis, etc.). Only in severe cases is the liver grossly enlarged enough to identify via palpation. Serum chemistries may be normal or may show mild elevation of ALT and GGT similar to lymphocytic hepatitis (see Lymphocytic hepatitis for discussion of serum chemistry evaluation). Radiographs or ultrasound may detect hepatomegaly (Chs 16, 17).

Diagnosis is via surgical inspection and/or biopsy. A transdermal biopsy may be performed if no surgery is elected. Grossly the liver appears pale brown to yellowish, and the lobes tend to be swollen and rounded.

Treatment includes controlling concurrent diseases (especially those causing weight loss), maximizing caloric intake, and minimizing liver pathology. If the patient is eating, supplement the normal diet with Hill's a/d canned food and a high calorie supplement such as Ferretvite, Nutrical, human Ensure, etc. to add calories. Anorexic animals can be force fed a/d and Nutrical unless vomiting. Broad spectrum antibiotics are safe and may inhibit GI bacterial overgrowth or low-grade suppurative hepatitis; a good combination is enrofloxacin at 5 mg/kg p.o. b.i.d. + amoxicillin at 10 mg/kg p.o. b.i.d. Ursodiol (Actigall) may be used to reduce biliary stasis, dosed at 15 mg/kg p.o. s.i.d. Prognosis is good with most ferret lipidosis patients, provided that the underlying cause of the lipidosis is identified and resolved.

End stage liver disease (cirrhosis)

This uncommon condition is the end result of chronic damage to the liver, most likely due to undiagnosed chronic hepatitis. At this stage, the liver is close to failing, and patients may present with either acute or chronic lethargy, nausea, vomition, diarrhoea, anorexia, icterus and weight loss. Patients who seem to become ill acutely may have acute bacterial hepatitis. The prognosis is poor once cirrhosis is confirmed.

Serum chemistries are compatible with liver damage *and* loss of function. Serum ALT and GGT may be mildly to markedly elevated and bilirubin is usually elevated also. AST and even alkaline phosphatase may elevate. Serum bile acids may be elevated as well. Lipase and globulin levels may be high with concurrent gut pathology (see Lymphocytic hepatitis and Inflammatory bowel disease for discussion of serum chemistry evaluation of hepatic and gut parameters, respectively).

A definitive diagnosis is made via biopsy. Ultrasound may detect changes in size and consistency of the liver suggestive of cirrhosis (Ch. 17). If biopsy is surgical, preoperative supportive care may be needed to strengthen and stabilize the patient prior to surgery. Antibiotics may produce significant improvement in signs and serum chemistries in some cases. Grossly, the liver appears small, firm, and irregular, sometimes with nodular regeneration visible. Histopathology shows bridging fibrosis with areas of regeneration, but overall loss of healthy hepatocytes. Underlying lymphocytic or neutrophilic inflammation may be noted.

The long-term prognosis is poor. Patients may be maintained on a high calorie low protein diet such as Hill's k/d feline; if needed one can mix in Hill's a/d diet or high calorie supplements such as Nutrical to improve palatability. Long term antibiotic therapy may be indicated, especially if histopathology revealed a suppurative component or the patient shows initial improvement on antibiotics. Long-term enrofloxacin dosed at 5 mg/kg p.o. s.i.d. may be enough to prevent re-infection. Ursodiol dosed at 15 mg/kg p.o. s.i.d. may also be used long term.

Biliary cysts and cystadenomas

These are histologically benign cystic structures located in one or more hepatic lobes; they are variable from small and focal to large and numerous. Dr Mike Garner (see p. 212) at Northwest ZooPath notes that they are common in both domestic and black-footed ferrets. Cystadenomas are benign but may be progressive in development; in extreme cases, the cystic masses may replace large portions of hepatic parenchyma in multiple lobes. In theory, if these lesions become extensive they could result in loss of hepatic function. However, few have resulted in clinical hepatopathy in the author's experience, and most often, the cystic masses were an incidental finding during a laparotomy. Large cysts may be palpable as soft masses in the cranial abdomen or may be visible on radiographs; smaller lesions may be detected via ultrasound (Chs 16, 17). No serum elevations of hepatic enzymes are usually seen; mild to moderate increases in ALT and GGT occasionally occur. Treatment (if elected) is surgical removal; in severe cases, the lesions may recur. Figure 9.10 shows moderately large biliary cysts in a necropsy specimen.

Hepatic neoplasia

Primary or metastatic neoplasms are occasionally seen in the ferret liver (Ch. 13). These are difficult to suspect unless detected via palpation, radiographs or ultrasound

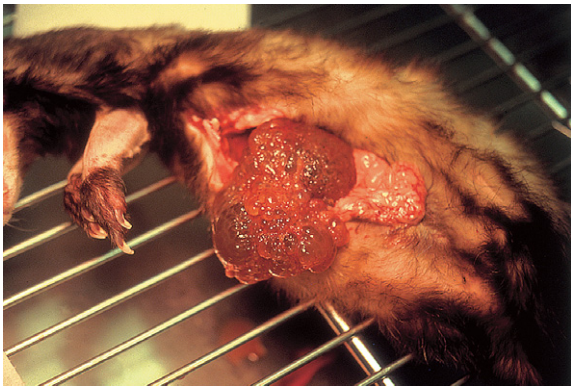

Figure 9.10 Large biliary cysts in a ferret; these were incidental findings and not the cause of death.

(Chs 16, 17). Clinical and serum chemistry findings resemble those seen with hepatitis. Neoplasia in the liver may also be suspected whenever severe elevations are seen in key serum chemistries, in particular ALT and GGT, and sometimes AST, alkaline phosphatase, or bilirubin. The main differential diagnosis is suppurative hepatitis (see Lymphocytic hepatitis for discussion of serum chemistry interpretation). The most common tumours seen in ferret livers are metastatic masses from other sites, mainly adrenal cortical adenocarcinomas and lymphomas. Both of these neoplasms tend to produce pale multiple masses when they involve the liver; some right adrenal tumours invade the caudate liver lobe locally without general metastasis (Fig. 9.11).

Primary hepatic masses are less common. They tend to be darker in colour, resembling the colour of normal liver to some extent. Several types are seen. *Helicobacter*-like organisms were reported associated with hepatitis

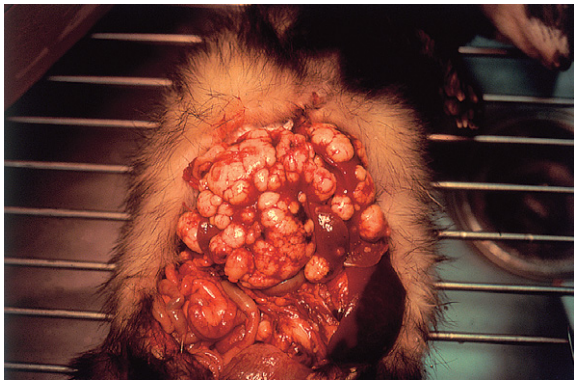

Figure 9.11 Metastatic adrenal cortical carcinomas in the liver of a ferret.

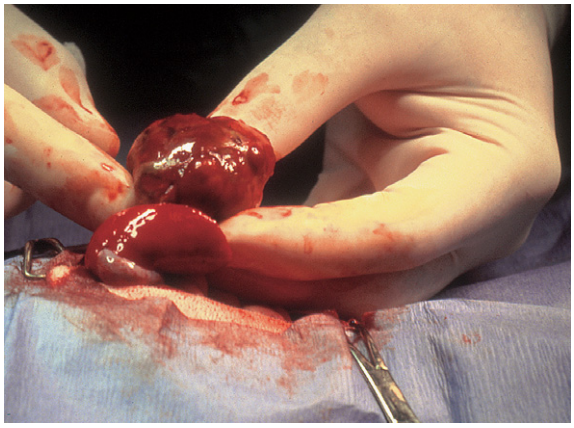

Figure 9.12 Hepatoma in a liver lobe; the single mass is elevated, showing the normal liver lobe it is attached to (below the mass).

and hepatic neoplasia in one study,[38] but none of our cases in the past 18 years have had similar findings.

Hepatomas are benign hepatocellular neoplasms which can produce clinical disease, either via damage to hepatic tissue and function, or possibly via inducing hypoglycemia. Hepatic neoplasms have been shown to be capable of inducing hypoglycemia in other species.[41,42,43] Clinical signs may include lethargy, salivation, weight loss, anorexia, bright orange-yellow or greenish urine (bilirubinuria), and icterus. Serum chemistries in an example case showed ALT = 1050 IU/L, AST normal, GGT = 37 IU/L, alkaline phosphatase normal, globulin = 3.6 g/dL and glucose = 38 mg/dL. Insulinoma is an obvious differential diagnosis for the hypoglycaemic component. Surgical findings are typically a single dark irregular liver-coloured mass involving one lobe, usually resectable (Fig. 9.12). Treatment is via excision; the prognosis is good.

Hepatocellular adenocarcinoma is a malignant aggressive neoplasm which may involve one or more lobes and may metastasize. Serum chemistries in a sample case showed ALT = 4035 IU/L, AST = 596 IU/L, GGT = 102 IU/L, alkaline phosphatase normal, lipase = 605 IU/L, globulin = 3.1 g/dL and glucose = 53 mg/dL. Treatment is via surgical resection if possible. Gross findings are one to many dark irregular liver-coloured masses involving one or more liver lobes, with visible metastasis sometimes seen. Solitary masses may be excised; with more aggressive lesions debulking the tumour mass might slow the clinical progression for a time. The prognosis is poor if the lesions are not detected early.

Biliary adenocarcinoma is occasionally seen. Findings and aggressive behaviour are similar to those of hepatocellular adenocarcinoma; treatment and prognosis are similar as well.

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