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# Diseases of the Gastrointestinal System

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## INTRODUCTION

In captivity, gastrointestinal (GI) diseases are widespread and the most common clinical finding in common marmosets [1–6]. Clinical signs may be due to a host of etiologies and typically manifest as weight loss, diarrhea, changes in eating habits, and/or abdominal distension. Proper recognition of clinical signs and identification of the underlying cause(s) is important to maintain the health of the individual animal and colony as a whole.

Marmosets are broadly characterized as frugivores, insectivores, and exudivores; and their GI system is adapted to meet the needs of this diverse diet [7]. Their teeth and bone structure allow them to gouge tree bark to eat edible plant exudates including gum, sap, and latex [8]. This gouging behavior not only exposes the sappy interior but also stimulates the plant to produce gum, thus resulting in a long-term food source [9,10]. To better digest the gums, marmosets have a large cecum for their body size, which enables efficient fermentation. They may also be able to preferentially retain liquids (i.e., gums) in the cecum while sending solid food to the colon, and their cecum has extensive folds and pockets that may allow for retention of bacteria to repopulate the upper colon when needed [11].

Marmosets in captivity are generally fed a commercial marmoset diet supplemented with fruit, vegetables, and insects or other sources of protein, such as eggs. Due to limitations in caging and diet formulation, the diet fed to captive marmosets likely does not recapitulate their natural diet, which can lead to nutrient deficiencies, secondary metabolic disorders, or inflammatory disease of the GI system. Care should be taken to avoid feeding diets high in simple sugars, such as glucose. While palatable, these diets can lead to secondary clinical problems, as noted below. While it was historically common to feed mouse pups to marmosets, this should be avoided due to the risk of disease transmission.

Additional detail on marmoset nutrition, including vitamin requirements, is discussed elsewhere in this volume. However, it should be noted here that marmosets have a dietary requirement for vitamin D3 due to a reported end-organ resistance [12]. Inadequate D3 levels in feed can result in osteomalacia or other bone pathology. This is covered in additional detail elsewhere in this volume.

Because clinical signs of GI disease are readily apparent to caretakers, veterinary staff are often tasked with identifying the potential causes of diarrhea in marmosets. Every investigation should begin with a thorough cageside examination to better understand the animal's temperament, activity level, and overall appearance. From there, a physical examination should be performed and include evaluation of the oral cavity and abdominal palpation. Veterinary staff should become familiar with the normal characteristics of marmosets including the thickness of the gut loops, liver size, and mesenteric lymph node size. Given their small size, it may be possible to perform a basic examination on awake, restrained animals. However, sedation enhances the ease through which abnormalities can be detected on abdominal palpation and reduces the risk of injuries to staff or animals.

In some cases a physical examination may allow proper diagnosis of a condition. However, additional diagnostics may be required. Radiography and ultrasonography are both readily available and easy to perform and can provide useful diagnostic information. Again, the clinician should become familiar with what is normal utilizing healthy animals as a baseline. There are also published resources available to describe normal radiographic and ultrasonographic anatomy [13,14].

Infectious causes of GI disease are not uncommon. Fecal bacterial culture is important when considering bacterial causes of GI diseases and many viruses can be identified through PCR or other techniques. Fecal

flotation, sediment analysis, or direct examination are useful to identify parasites and protozoa.

More advanced diagnostics such as colonoscopy and biopsy may also be considered and can provide useful diagnostic information for some bacterial, viral, neoplastic, or inflammatory conditions. Intestinal biopsy with or without colonoscopy is easily performed utilizing pinch biopsy forceps with an opening measuring approximately 4 mm. Liver biopsy can be obtained percutaneously or via a small paracostal incision.

In those institutions maintaining colonies of marmosets, consideration should be given to longitudinal tracking of colony health. Tracking body weight and body condition scores is a simple method that can provide useful long-term data on colony health. More complex analyses of body composition, such as EchoMRI or DEXA scans, can also be used and may be simple to perform in marmosets trained to cooperate. This is covered in more detail elsewhere in this book. These modalities can provide useful information to track changes in fat, lean mass, and bone composition over time to evaluate changes in colony health and may be able to identify subtler changes.

Finally, necropsy of index cases also serves as a useful diagnostic tool, especially in larger colonies. A complete and thorough necropsy provides valuable diagnostic information that may not be obtained through other methods. Necropsy examination should be performed by a trained pathologist or person familiar with normal marmoset anatomy and abnormal tissues should be submitted for histopathologic evaluation. Additionally, in the event of an epizootic, euthanasia of affected animals may help limit the spread of the agent, thereby preserving the health of the remainder of the colony.

The GI tract is large and encompasses different organ systems, each of which has its own spectrum of common diseases. Each system will be covered individually below. In addition, specific detail on the multisystemic manifestation of some diseases may be found in other chapters of this manuscript.

## DISEASES OF THE ORAL CAVITY AND ESOPHAGUS

Examination of the oral cavity should be a part of every physical examination. Traumatic injuries to the teeth are common and should be identified and treated appropriately to prevent continued oral pain or ongoing pathology.

### Teeth

Marmosets have a symmetrical upper and lower tooth arcade with two incisors, one canine, three

premolars, and two molars. Detailed descriptions of the order of tooth eruption have been published [15,16]. They are specially adapted to eat plant exudates and in the wild may spend up to 30%–67% of their time foraging for exudates. To aid in this endeavor, they use specially adapted teeth [8].

### Dental Fractures and Abscesses

Tooth damage is a common source of morbidity in captive marmosets. Any damage that exposes the root cavity may lead to bacterial infection and a resultant abscess. A common cause of damage is tooth fracture as a result of handling, but wear from enrichment devices, cage material, or other sources may also lead to dental wear and eventual exposure of pulp cavity.

Marmosets with damage to upper teeth present with facial swelling on their cheek, lateral to the nares and below the eye (Fig. 13.1). This is sometimes associated with oculonasal discharge. Damage to lower teeth is less common but can result in abscess formation on the chin or upper neck. Swelling often begins as a red discoloration, progressing rapidly to abscess formation and purulent exudate. Bacterial isolates from the lesions vary, and bacteria may invade the maxilla which will be evident radiographically [17]. Treatment often requires removal of the affected tooth to allow drainage (Chapter 10 of this volume, figures 10 and 11) with subsequent antibiotic treatment to prevent osteomyelitis, damage to the orbit or globe, or sepsis.

### Periodontal Disease

Periodontal disease is also a common problem in captive marmosets. Animals have varying clinical signs of gingivitis, hyperemia, pocket formation, and tooth loss [5]. The exact etiology is not described in the



**FIGURE 13.1** Tooth root abscesses often present with facial swelling on their cheek, lateral to the nares and below the eye.

literature, but one would presume that dietary factors including reduced mechanical cleaning of teeth due to reduced tree gouging behavior may play a role. A variety of bacterial isolates may also be present. Periodic dental examinations during routine preventive health assessments along with prophylactic cleaning should be performed to prevent gingivitis and periodontal disease.

## Viral Infections

While marmosets may be susceptible to a wide range of oral viral pathogens, by far the most important are herpes infections. These agents can cause significant morbidity and mortality, which can greatly affect captive colonies. Care should be taken to avoid infection by strictly separating callitrichids from other species of New World monkeys.

### **Herpes Simplex**

*Etiology:* Human herpesvirus 1 (HHV-1) (herpes simplex virus) has been identified as the cause of outbreaks of vesicular stomatitis in common marmosets. In all cases, animals have been exposed to a caretaker with recrudescing herpesvirus lesions several days earlier.

*Clinical signs:* HHV-1 infection is rapidly progressive and animals may die within 1–4 days [18]. Clinical signs include ulcerative lesions on the tongue, gingiva, and lips, which are associated with anorexia, weakness, and hypersalivation. More rarely, signs may progress to include more fulminant signs such as seizures [18,19].

*Pathology:* Pathology findings are consistent with the clinical signs and include vesicular and ulcerative lesions of the oral and esophageal mucosa. Inflammatory exudate and intranuclear inclusion bodies are associated with these lesions. Animals that live longer may develop meningoencephalitis [19].

*Prevention and control:* Due to the potential for this virus to spread from animal to animal within a colony, suspected cases should be euthanized immediately and submitted for pathologic examination. Contact animals should be quarantined and observed closely for clinical signs to prevent the spread of disease to other animals in the group. Caretakers with suspect clinical signs should be assigned alternative work duties to prevent exposure of the colony.

### **Herpes Tamarinus**

*Etiology:* *Herpesvirus tamarinus* is an alphaherpesvirus related to *Herpes simplex* whose natural host is the squirrel monkey [20]. Spider monkeys and some animals in the genus *Cebus* may also be latent carriers [21]. Though rarely a source of disease in squirrel monkeys, it causes ulcerative and vesicular stomatitis in aberrantly infected callitrichids [22].

*Clinical signs:* The disease course and clinical signs are similar to that noted for *Herpes simplex*, with a short incubation period and relatively rapid progression to death. In addition to stomatitis, infection is associated with hepatosplenomegaly, ulcerative gastroenteritis, and multifocal necrosis in the adrenal glands, liver, and lymphoid tissue.

*Pathology and diagnosis:* Clinically apparent oral vesiculation and ulceration should cause a high level of suspicion, and diagnosis can be achieved by biopsy or through viral isolation from saliva. Biopsy will show ulcerative and vesicular lesions with suppurative inflammation, viral syncytia, and intranuclear viral inclusion bodies.

*Prevention and control:* Treatment with antiherpetic drugs has not been reported, and consideration should be given to euthanize infected animals, and potentially their contacts, to limit the spread of the agent and prevent an epizootic. Because of the risk of this virus, there should be strict separation of callitrichids from other New World primate species. Suspected cases should be euthanized for a diagnostic evaluation including necropsy and histopathology, and contact animals should be quarantined and closely observed.

## Fungal Disease

*Candida albicans* can infect marmosets but is generally only associated with disease in debilitated animals in whom it may cause thrush [23,24]. Thrush is characterized by a white discoloration and proliferation on the tongue and in the esophagus. Lesions are most common in the upper GI tract but may be present in other regions as well. Oral nystatin wash or fluconazole may be effective, and treatment aimed at eliminating the cause of debilitation or immunosuppression should be initiated.

## Neoplastic Diseases

In general, neoplastic diseases of the oral cavity are rare in nonhuman primates, including common marmosets. There is, however, a report of oral and nasopharyngeal squamous cell carcinoma affecting eight animals (4.9%) in a single colony [25]. These tumors were locally invasive with expansion into the jaw and/or palate, retrobulbar space, or base of the cranium. While a similar incidence of this specific neoplasm has not been reported elsewhere, it should be included as a differential diagnosis for oral proliferative lesions.

## Nutritional Diseases

As in other primate species, marmosets should be provided a balanced diet containing essential nutrients



and vitamins. With respect to oral health, vitamin C and niacin are both essential to maintain the integrity of the oral mucosa.

Vitamin C is required to cross-link collagen and therefore an essential dietary nutrient in species lacking gulonolactone oxidase, including marmosets. Deficiency (scurvy) affects multiple species of primates. Marmosets have been reported to have a relatively high requirement for vitamin C and to develop clinical signs after approximately 10 weeks of absolute restriction.

Clinical signs include weight loss, altered gait, and gingival hemorrhage. At necropsy, animals may have hemorrhages around joints and in muscles. Histologically, there was prominent hemorrhage around the periodontal ligament despite not having the characteristic gingivitis that plagues other species of primates [26–29].

To prevent this disease, animals should be fed a commercial diet with adequate levels of vitamin C. Care should be taken to monitor the shelf life and refrigerate diets according to the manufacturer's recommendations to prevent loss of vitamin C over time and secondary nutritional deficiency. Animals that develop clinical signs should be treated with dietary supplementation of at least 500 ppm and by injection of vitamin C, but marmosets may be refractory to treatment [27].

Other nutrient deficiencies may also manifest as oral disease including vitamin A [30], folic acid [31], and niacin [32] deficiencies. Vitamin A deficiency causes aberrant epithelialization and keratinization of the oral mucosa. Folic acid deficiency causes impairment of keratinization and secondary ulceration, which results in weight loss and anorexia. When the related species *Saguinus oedipus* was fed a diet deficient in niacin, animals developed ulcerative stomatitis, ulcerative enterocolitis, and ulcerative and atrophic glossitis [32]. Clinical signs included anorexia and weight loss as a result of the extensive oral and intestinal lesions. Prevention of all of these syndromes can be accomplished through provision of a well-balanced diet.

### Congenital Malformations

Though rare, clinicians should be cognizant of potential congenital malformations in marmosets that are aborted near full gestational age or that die soon after birth. Recently, one marmoset breeding colony in the United States had three cases of cleft palate. In all cases, animals developed to full term. One was still-born, one died perinatally, and one lived to 4 days old but eventually died. No other malformations were present [33]. There has also been a single case report of cleft palate in an aborted brown-mantled tamarin fetus [34]. In another report, a single animal was born with cleft lip and cleft palate, microphthalmia, and polydactyly. The

animal was born at full term but euthanized after being rejected by its parents. Together, this triad of congenital malformations suggests 13 trisomy [35].

## DISEASES OF THE STOMACH AND INTESTINE

Diseases affecting the stomach and intestine of marmosets are the cause of significant morbidity and mortality in marmoset colonies around the world. Often the presenting complaint is diarrhea. Utilization of a scoring system to track diarrhea longitudinally may prove useful, and such systems have been published [36]. Clinicians should become familiar with the common causes of diarrhea and weight loss and pursue diagnostic tests as appropriate to each case.

### Bacterial Diseases

Scientific reports of bacterial enterocolitis in common marmosets are surprisingly rare. Marmosets are likely as susceptible to a similar variety of GI pathogens as other primates, including humans. If a bacterial disease is identified, care should be taken to ensure overall colony health by identifying and treating subclinical carriers in addition to those animals with recognizable clinical signs. In addition, many of these pathogens are zoonotic risks, highlighting the need for personal protective equipment and strict sanitation.

### *Escherichia coli*

*Etiology:* *Escherichia coli* is a Gram-negative bacillus that includes a diverse array of serotypes and pathogenic subtypes. Enteropathogenic *E. coli* positive for the attaching and effacing locus have been responsible for outbreaks of hemorrhagic diarrhea in common marmosets and related species [37–40]. In two reports, *E. coli* was positive for the attaching and effacing (*eae*) gene, negative for shiga toxin production, and were identified as serogroup O26. This serogroup is associated with outbreaks of diarrhea and hemolytic uremic syndrome in man and thus represents a potentially serious zoonotic threat to caretakers [38].

*Clinical signs:* Clinical signs in infected animals include weakness, lethargy, dehydration, and voluminous watery diarrhea that progresses rapidly to include hemorrhage [39,40]. Individual cases, or, commonly, outbreaks of diarrhea, should cause a high index of suspicion. Anecdotally, some animals may present with red-tinged urine as well.

*Pathology:* Intestinal biopsies or samples of intestine from necropsy will show mucosal erosion, adherent bacillary bacteria, and a cobblestone appearance to the

mucosa. This attaching and effacing lesion is pathognomonic and may aid in the rapid diagnosis of infection.

**Diagnosis:** Diagnosis can be made through fecal culture on MacConkey agar, and *E. coli* culture should be specifically requested from the diagnostic lab. If *E. coli* is cultured, serotyping can be pursued to identify the exact etiology and relative risk to humans.

**Prevention and control:** Prevention of the introduction and spread of disease should be accomplished through washing of fruits and vegetables fed to animals, hygiene of caretakers, and strict use of personal protective equipment. Treatment should be initiated based on bacterial sensitivity results, but empirical selection of enrofloxacin dosed orally or parenterally is normally effective.

### **Klebsiella pneumoniae**

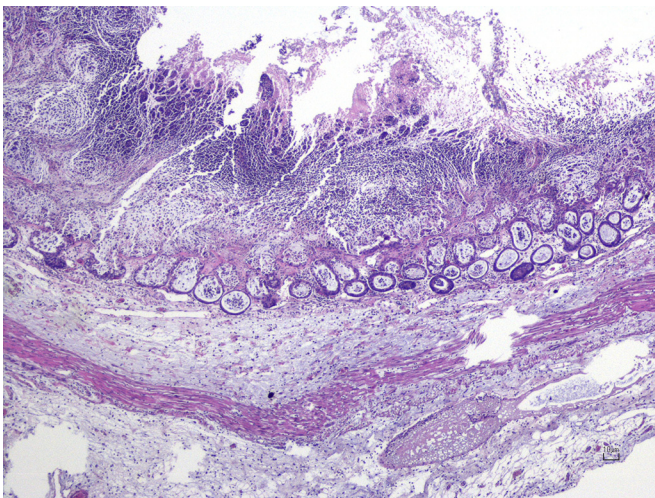
**Etiology:** *Klebsiella pneumoniae* is a Gram-negative bacillus that has been associated with outbreaks of fatal peritonitis and GI disease in common marmosets [1,2,41,42] and other New World primates [43].

**Clinical signs:** In marmosets, clinical signs include anorexia, mesenteric lymphadenopathy, diarrhea, and peritonitis.

**Pathology:** At necropsy, animals generally have ulcerative colitis and fibrinopurulent peritonitis with bacterial septicemia and dilated colonic crypts (Fig. 13.2).

**Diagnosis:** Diagnosis is readily made through culture, and sensitivity testing should be performed as bacteria may harbor resistance genes.

**Prevention and control:** Treatment with enrofloxacin should be rewarding unless the particular strain is resistant. Consideration should be given to screening contact animals with nasopharyngeal and/or rectal cultures and treating any animals identified as carriers with an appropriate antibiotic.



**FIGURE 13.2** *Klebsiella* causes severe disease with ulcerative colitis, fibrinopurulent peritonitis, and septicemia. Hematoxylin and eosin, 40x. Image courtesy of Charles Bailey, Johns Hopkins University.

### **Shigella sp.**

**Etiology:** *Shigella* sp. are common pathogens of laboratory primates. Shigellosis is highly contagious and inoculation with as few as 10 organisms may cause infection [44]. Shigellosis is less commonly reported in marmosets than in other nonhuman primate species, but infection with *Shigella sonnei* has been reported [23,37].

**Clinical signs:** Clinical signs include depression, lethargy, and dehydration due to ongoing hemorrhagic diarrhea. Facial edema, likely due to fluid imbalance, may also be seen.

**Pathology:** At necropsy, animals will have necrotizing, hemorrhagic, and ulcerative typhlocolitis, similar to the pathology of other nonhuman primates with shigellosis.

**Diagnosis:** Diagnosis is made through fecal culture. However, laboratory misdiagnosis is not uncommon, and there is some difficulty in distinguishing *E. coli* and *Shigella* [44]. In an outbreak situation, consideration should be given to utilizing alternative diagnostic modalities such as PCR to properly identify the etiologic agent.

**Prevention and control:** In the cited report, treatment with neomycin was effective; however, one should consider utilizing enrofloxacin or trimethoprim-sulfamethoxazole, which is utilized with success in other species including man [44]. Due to the risk to other animals and zoonotic potential for this pathogen, care should be taken to isolate infected animals, utilize rigid personal protective equipment practices, and properly sanitize the environment. Treated animals should be cultured or examined by PCR following cessation of therapy to identify any residual carriers. These animals should undergo further treatment until cultures and/or fecal PCR show elimination of the carrier state.

### **Helicobacter sp.**

Various species of *Helicobacter* have been isolated from marmosets including *Helicobacter jaachi*, *Helicobacter callitrichis*, and others [45–47]. Due to the nature of the surveys conducted, a correlation with any specific clinical sign or disease syndrome is not possible. In one survey [45], identification of *Helicobacter* sp. histologically was not associated with pathologic changes in the stomach.

### **Clostridium perfringens**

**Etiology:** *Clostridium perfringens* is an anaerobic spore-forming, rod-shaped bacterium associated with gas gangrene in a variety of species. There are scant reports of *Clostridium perfringens* causing anorexia, diarrhea, gas gangrene, and death in marmoset colonies including one in which 29 animals died due to gastric dilation following antibiotic treatment for shigellosis [48,49].



**Clinical signs:** Animals may develop facial swelling and facial erythema. Death is often rapid and sudden, and the GI tract is distended by gas.

**Pathology:** The intestines, in addition to gas, contain watery brown-gray fecal material and may also have areas of necrosis and mucosal sloughing. Bacteria can be identified in GI contents. In addition, organisms may be identified circulating in the blood and within various tissues, including muscle, bile ducts, liver, lungs, and kidney.

**Prevention and control:** Given the rapid clinical course, animals may die without premonitory clinical signs. If a diagnosis is made, treatment with antibiotics such as clindamycin, rifampin, or tetracycline should be considered. Prophylactic treatment of other potentially exposed animals may help prevent additional deaths due to this disease.

### **Clostridium difficile**

*Clostridium difficile* may also be associated with disease but is rarely reported. A high index of suspicion should occur if animals develop diarrhea following antibiotic therapy. Affected marmosets develop bloody diarrhea, weakness, and collapse. Antibiotic therapy alters the normal gut microbiota and allows proliferation of toxin-producing *C. difficile*. At necropsy, lesions range from mild mucosal edema to pseudomembranous colitis. Transmural cecal and colonic necrosis may also be seen [50–52].

### **Yersinia sp.**

*Yersinia enterocolitica* is a Gram-negative coccobacillus that causes gastroenteritis in humans. *Y. enterocolitica* and its relative *Y. pseudotuberculosis* have been reported in other species of primates; and while rarely reported in marmosets, it can cause diarrhea [3,53,54]. The most prominent pathologic change is hepatic necrosis, but there may also be necrosis in the small and large intestines. Diagnosis can be achieved through histologic findings of index cases, fecal culture, or PCR. Treatment may be unrewarding but should include supportive care and aggressive antibiotic therapy with fluoroquinolones or trimethoprim–sulfamethoxazole.

### **Mycobacteria sp.**

Atypical mycobacterial species, including *Mycobacterium kansasii* and *Mycobacterium gordonae*, can be isolated from the GI tract including stomach fluid and feces [55]. While not associated with clinical GI disease, bacteria are associated with mesenteric lymphadenitis, and enlarged abdominal lymph nodes can sometimes be palpated. Perhaps most importantly, atypical mycobacteria can cause positive reactions to tuberculin skin tests

in marmosets and therefore must be distinguished from *Mycobacterium tuberculosis* infection.

### **Parasitic Diseases**

While parasitic diseases were very common historically, changes in husbandry including the use of antiparasitic drugs and effective pest control have reduced their burden in many marmoset colonies.

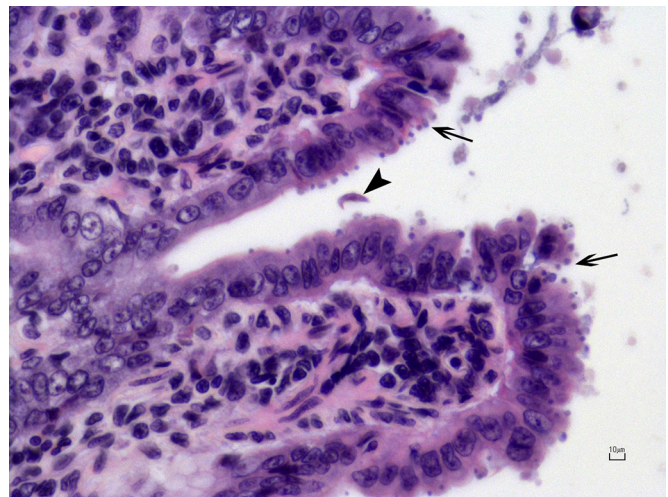
#### **Giardia sp.**

**Etiology:** *Giardia* is a flagellated protozoan parasite.

**Clinical signs:** *Giardia* sp. has been identified as a common organism in the feces of marmosets but is not generally associated with immediate clinical signs. It may be more common in animals <1 year of age [36,56].

**Diagnosis:** Diagnosis can be accomplished through ELISA of fecal specimens, and testing of colonies may show a high prevalence of infection despite a lack of appreciable clinical signs. Direct examination of fecal flotations can also be used but is less sensitive than immunoassays. Organisms can also be identified histologically as small crescent-shaped or teardrop-shaped organisms with paired nuclei in the lumen (Fig. 13.3). Regardless of the diagnostic methodology chosen, multiple samples should be sampled over the course of several days due to intermittent shedding.

**Prevention and control:** Eradication with two doses of oral tinidazole was effective at eliminating the disease and this was associated with weight gain 1 year later. This suggests that elimination of *Giardia* sp. from colonies is worthwhile to improve the overall colony health and may help reduce the incidence of unexplained



**FIGURE 13.3** *Cryptosporidium* sp. and *Giardia* sp. can both cause diarrhea or may be seen in asymptomatic animals. *Cryptosporidium* can be visualized as small basophilic organisms at the luminal surface of the small or large intestine (arrows). *Giardia* often appears as small crescent-shaped organisms within the lumen (arrowhead). Hematoxylin and eosin, 600x. Image courtesy of Charles Bailey, Johns Hopkins University.

weight loss, which is generally associated with inflammatory bowel disease (IBD) [36].

### **Coccidia**

*Isospora arctopitheci* can infect marmosets. Parasites invade the small intestinal epithelium and, while most infections remain subclinical, may cause clinical signs including bloody diarrhea. In severe infections, animals may die between 3 and 7 days post infection. Oocysts can be identified on fecal flotation or sedimentation. At necropsy animals will have small intestinal lesions characterized by sloughing of the intestinal epithelium. Sporocysts, macrogamonts, and microgamonts are usually visualized in epithelial cells at the distal end of intestinal villi, especially the jejunum. Mice serve as an intermediate host; and therefore, feeding of mouse pups to marmosets should be avoided [57–59].

### **Prosthenorhis elegans**

*Prosthenorhis elegans* attaches to the wall of the ileum where it forms a fibrous nodule and is associated with inflammation near the site of attachment. In some animals, there may be adhesions between the ileum and adjacent structure, abscess formation, or septic peritonitis resulting from partial rupture of the ileum [60,61]. Depending on the degree of inflammation and adhesion formation, animals may present with no clinical signs or they may present with abdominal turgor, lethargy, weakness, or signs of sepsis.

### **Other**

*Entamoeba coli* may be present in the GI tract but is not often associated with disease and is considered, like in other primate species, nonpathogenic in most cases.

*Cryptosporidium parvum* is a known pathogen of a variety of species and has been reported in symptomatic and asymptomatic marmosets [56,62]. On histology, small, round, blue organisms are seen at the luminal surface (Fig. 13.3). Treatment with paromomycin has proven effective.

## **Viral Disease**

### **Morbilliviruses**

**Etiology:** Morbilliviruses are RNA viruses associated with disease in a variety of species. The most common *Morbillivirus* is measles virus, which is the cause of significant morbidity and mortality in primates.

**Clinical signs:** In Old World monkeys, it is associated with a multisystemic disease centered on the skin, lymphoid system, brain, and lung. Unlike Old World primates and man, callitrichids infected with either measles or the closely related *Paramyxovirus saguinus*

usually develop a GI syndrome characterized clinically by diarrhea, dehydration, and progressive lethargy. However, upper eyelid edema, a skin rash, and pneumonia can also be seen [63].

Experimentally infected mustached tamarins generally succumbed within 2 weeks of infection [64]. Outbreaks have been reported in several species of callitrichids with up to a 100% mortality in some species [63,65]. In these situations, death may occur as soon as 8 h after onset of clinical signs and not all animals will show clinical signs.

**Pathology:** Gross pathology findings include hemorrhagic gastroenteritis and colitis and variable pneumonia. Histologically, there is multifocal necrotizing gastroenterocolitis and/or bronchointerstitial pneumonia depending on the tropism of the specific virus. Large syncytial cells containing intranuclear and intracytoplasmic viral inclusions may be present in the gut, bile ducts, pancreatic ducts, renal tubules, bronchial epithelium, or hepatic cords; and there may be necrosis of lymphoid tissue, which is typical of morbillivirus infection.

**Prevention and control:** Based on these reports and clinical knowledge of the disease in man, every effort should be made to prevent entry of measles virus into research colonies. Contact with personnel should be limited to those who have been vaccinated and/or screened for positive antibody titers. If an outbreak does occur, affected animals should be quarantined and consideration should be given to culling affected animals early to help limit the spread of disease.

Vaccination is a common practice in colonies of macaques and other Old World primates. Marmosets have been successfully vaccinated [64]. While routine vaccination does not appear to be a common practice, vaccination with the human measles or canine distemper-measles vaccine should be considered to protect colony health in an epizootic. Treatment of affected animals, if attempted, should include rehydration, supportive care, and antibiotics to treat and prevent secondary infections.

### **Herpesvirus ateles and Herpesvirus saimiri**

**Etiology:** *Ateline herpesvirus 2* and 3 (*Herpesvirus ateles*) is a gammaherpesvirus in the genus *Rhadinovirus* related to Epstein–Barr virus (EBV) whose natural host is the spider monkey [66–68]. When experimentally inoculated in common marmosets, it causes Hodgkin's-like lymphoma, which may manifest as GI disease due to proliferation of neoplastic lymphocytes in the gut and abdominal lymph nodes.

*Saimiriine herpesvirus 2* (*Herpesvirus saimiri*) is a closely related herpesvirus whose natural host is the squirrel monkey. In squirrel monkeys, it is not generally associated with disease but can persistently infect marmoset



lymphocytes and cause malignant transformation [66,67,69–71].

**Clinical signs:** For both agents, disease has been reported to start approximately 2–3 weeks postinoculation and may prove fatal by 3–4 weeks; but longer courses with slower-growing lymphomas have also been described. Disease is characterized by a mild-to-moderate leukocytosis, circulating neoplastic cells visible on blood smears, generalized lymphadenopathy, and hepatosplenomegaly. Animals may also have upper respiratory disease including nasal discharge.

**Pathology:** At necropsy, there is diffuse lymphoma affecting multiple organs that can include those noted above plus kidney, adrenal gland, tonsils, and lung. Aggressive cases may also be associated with extensive hemorrhage and necrosis in vital organs. Treatment has not been described though animals have been vaccinated using an attenuated viral strain. Vaccination successfully protected animals from subsequent challenge [72].

**Prevention and control:** Because of the risk of this virus, there should be strict separation of New World primate species. Suspected cases should be euthanized for a diagnostic evaluation including necropsy and histopathology, and contact animals should be quarantined and closely observed.

### **Other Gammaherpesviruses**

*Human herpesvirus 4* (EBV) causes mononucleosis, lymphoma, and nasopharyngeal carcinoma in people. While infection to callitrichids has been documented, common marmosets seem relatively resistant to lymphoma development following EBV infection [73,74]. However, some strains may be more or less oncogenic, and EBV/HHV-4 should be considered as a differential diagnosis for malignant lymphoma in the marmoset [69]. Animals that do progress to lymphoma have a more protracted course than with *Herpesvirus ateles* or *saimiri* with lymphoma developing 4–8 weeks post infection.

Finally, *Callitrichine herpesvirus 3* (CalHV3) has also been associated with GI lymphoma, although an etiologic relationship has not been established. Animals develop clinical signs including inappetence, diarrhea, and weight loss and often have palpable abdominal masses. At necropsy, B cells invade the gut and cause enlargement of mesenteric lymph nodes. While seroprevalence may be as high as 60% in some colonies, the incidence of GI lymphoma may be low [75–77]. Currently it is not clear whether CalHV3 is the etiologic agent responsible for these lymphomas or if it is detected in these lesions because of their high B-cell content.

### **Other**

Experimental infection with the SARS coronavirus has been reported and resulted in diarrhea associated with mild diffuse colitis. At necropsy, animals had colonic crypt hyperplasia [78]. Experimental yellow fever infection has been associated with hemorrhagic diarrhea and melena, with findings of hemorrhagic gastroenteritis at necropsy [79,80].

## **Neoplastic and Proliferative Disease**

### **Small Intestinal Adenocarcinoma**

The most common GI tumor of common marmosets is small intestinal adenocarcinoma [81–83]. Tumors generally originate in the proximal jejunum but may also be present in the distal jejunum or ileum. Metastasis to the mesenteric lymph nodes is common and has also been reported in the lung and kidney.

Not surprisingly, the most common clinical signs are diarrhea and weight loss, though animals may also present with abdominal bloat. At necropsy, there is focal thickening of the small intestine with or without stricture. In man, gastric carcinomas have been associated with EBV infection and with *Helicobacter* sp. infection. Neither was identified as a potential cause for small intestinal adenocarcinomas in the largest report to date [83]. Based on these results, small intestinal carcinoma should be considered as a differential diagnosis in cases of diarrhea for which another underlying cause cannot be identified.

### **Gastrointestinal Lymphoma**

GI lymphoma is not uncommon and may be associated with a viral cause including *Callitrichine herpesvirus 3*, *Herpesvirus saimiri*, *Human herpesvirus 4* (EBV), or *Herpesvirus ateles* as described above.

### **Other**

Reports of other proliferative diseases in common marmosets are exceedingly rare. There is a single case report of an inflammatory fibroid polyp in the duodenum of a common marmoset [84].

## **Other Noninfectious Diseases**

### **Inflammatory Bowel Disease**

**Etiology:** No discussion of GI disease in common marmosets would be complete without the discussion of IBD. In marmosets, this condition has historically been called marmoset wasting syndrome (MWS). In reality, the historical MWS is most likely a group of distinct disease entities that present with similar clinical signs but diverse etiologies and associated pathology [41]. Because MWS lacks diagnostic specificity, its use should

be discouraged and marmoset diseases causing significant weight loss or wasting should be referred to by their etiology or associated morphologic changes. IBD is a known entity and will be described further.

**Clinical signs:** Clinical signs for both small and large intestinal IBDs are apparently similar in marmosets. Clinically, IBD animals present with diarrhea, weight loss, alopecia, and a failure to thrive. Bloodwork may show hypoproteinemia, anemia, and elevated liver enzymes [85]. As the condition progresses, animals may develop muscle atrophy and weakness, including a characteristic facial appearance with prominence of the cranium and ears.

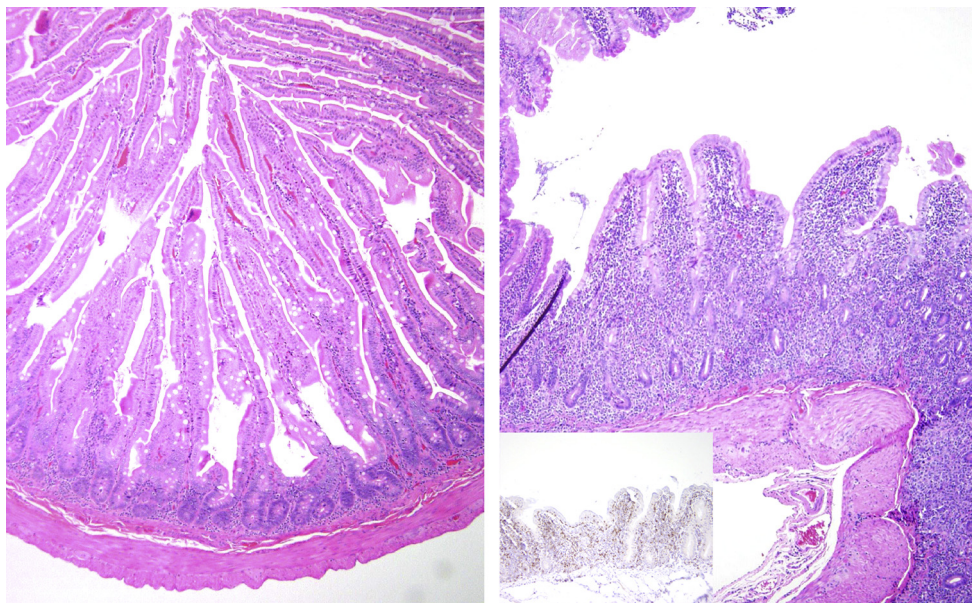
**Pathology:** Simplistically, there are two general pathologic patterns of IBD. Historically, IBD in callitrichids has been associated with chronic colonic inflammation in which the lamina propria is expanded by lymphocytes [1,4,60,85,86]. While most associated with tamarins [1,60], this has also been shown to commonly affect adult common marmosets [1,2,4]. Other reports discuss a chronic lymphocytic enteritis (CLE) centered on the small intestine (Fig. 13.4). Histologically, the lamina propria of the jejunum is expanded by lymphocytes and villi are blunted [2,41,86,87].

A specific entity of IBD has been recognized in some common marmoset colonies characterized by a CLE accompanied by progressive weight loss. In this form of IBD lymphocytic infiltrates comprising CD3/CD56-positive cells efface the normal architecture resulting in fusion and blunting of villous tips accompanied by crypt hyperplasia. Intense lymphocytic infiltration of the epithelium is observed consistent with an

immune-mediated response to environmental or potentially host antigens [41]. Treatment with prednisone and dietary withdrawal of gluten had no effect on the clinical disease. Elimination of *Giardia* within the colony was associated with a marked reduction in incidence of the disease, suggesting that environmental triggers may initiate a self-perpetuating immune-mediated disease.

**Differential diagnosis:** Despite the high prevalence of the disease and associated morbidity and mortality, the definitive cause of IBD/CLE has yet to be identified. Weight loss and wasting are nonspecific signs in marmosets and may be associated with a number of clinical entities. These findings have been associated with parasitic infection [36,88–90], gluten sensitivity [91], dietary protein deficiency [92,93], vitamin E deficiency [23], stress, and gliadin hypersensitivity [94,95]. In one survey of zoos, no fewer than 10 causes were proposed by survey respondents [96]. In some cases, subsequent investigations have contradicted previous assertions [97].

As noted earlier, wild marmosets obtain a large percentage of their calories from tree exudates and neither this method of foraging nor the nutritional content of the exudate are exactly recapitulated in current marmoset diets. Additional investigations into dietary factors would be worthwhile. Recent reports of gluten sensitivity including elevations in anti-*Gliadin* antibodies and positive response to food trials eliminating gluten indicate that dietary factors, specifically incorporation of cereals into the diet, may play a role in the development of IBD [91,94,95]. Furthermore, in one



**FIGURE 13.4** Compared with normal marmosets (left), animals with chronic lymphocytic enteritis (right) have villous blunting and fusing with expansion of the lamina propria by large numbers of CD3+ lymphocytes (inset). Hematoxylin and eosin, 100x. Images courtesy of Keith Mansfield, Novartis Institute for Biomedical Research.



experiment, wild-caught *Saguinus* sp. monkeys were biopsied at baseline then placed in a standard cage and fed a commercial diet. They developed characteristic colonic inflammation during the course of captivity, which would seem to implicate food and/or stress [98].

**Diagnosis:** Regardless of the cause, IBD poses a unique threat to captive marmoset colonies and represents a significant cause of mortality [99]. Diagnosis is often made through identification of clinical signs but gut biopsies can also prove useful. Recently, calprotectin and matrix metalloproteinase 9 have been identified as possible biomarkers of disease in marmosets [100,101]. Additionally, hypoalbuminemia (<3.5 g/dL) and weight loss (<325 g) together are negatively correlated with outcome [102].

**Prevention and control:** Treatment should be supportive. Some success has also been reported in treating animals with glucocorticoids. Due to the possible side effects of this and effects on research, long-term glucocorticoid therapy may not be possible in many situations but could be considered for individual cases [103]. Elimination of other causative factors such as parasitic infections should be pursued and animals should be fed a nutritious and balanced diet formulated for their species.

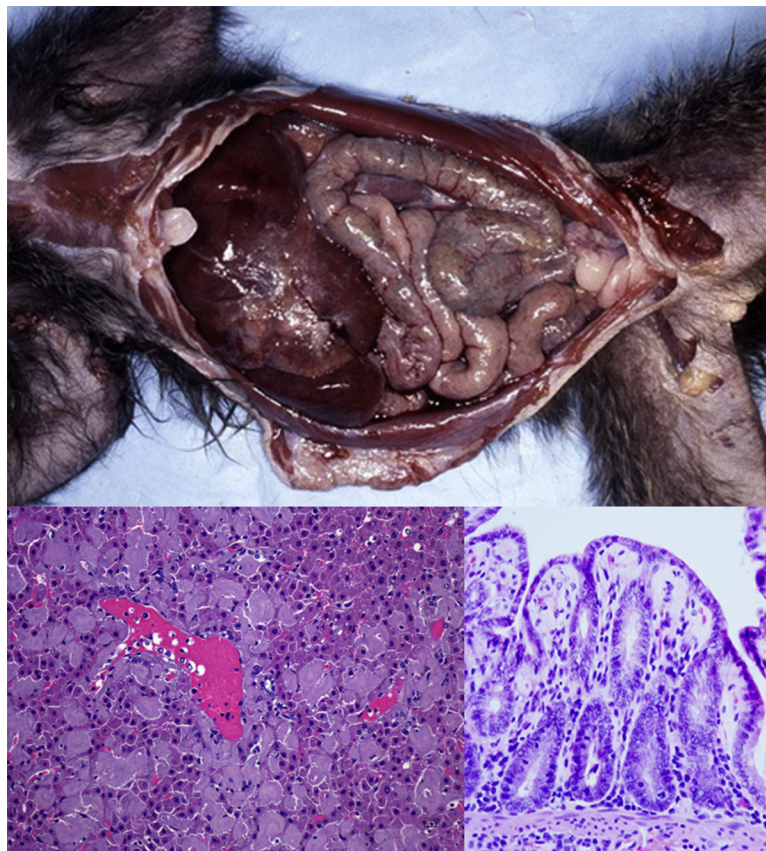
### **Amyloidosis**

While IBD is a major source of mortality in animals <6 years of age, amyloidosis is more common in older animals [99] and in one survey affected 17% of animals overall. Amyloid was identified as AA or reactive amyloid that originates from the N-terminal fragment of the serum amyloid A (SAA) protein [104]. Animals with reactive amyloidosis tend to be older (6.75 years of age) compared with animals that die of other causes and present with weight loss with or without diarrhea and hepatosplenomegaly. Organs affected include, in decreasing order of frequency, the small intestine, liver (Fig. 13.5), adrenal glands, kidney, stomach, colon, and spleen. In some animals, diagnosis can be confirmed through use of rectal biopsy or percutaneous liver biopsy.

## DISEASES OF THE LIVER

### **Bacterial Diseases**

Bacterial liver disease in marmosets is uncommon but has been reported both naturally and experimentally.



**FIGURE 13.5** Amyloidosis commonly affects the liver and intestine. Livers appear large, pale, and waxy. The gut is thickened and tortuous. Histologically, amyloid is identified as extracellular amorphous eosinophilic material, which expands hepatic sinusoids and/or the lamina propria of the small or large intestine. Hematoxylin and eosin, 400x. Images courtesy of Keith Mansfield, Novartis Institute for Biomedical Research and Charles Bailey, Johns Hopkins University.



## Clostridium piliforme

*Etiology:* *Clostridium piliforme* is a rod-shaped, flagellated, anaerobic, spore-forming bacillus that is the causative agent of Tyzzer's disease. Tyzzer's disease can infect a wide range of laboratory animals and has been reported in both marmosets and tamarins.

*Clinical signs:* Animals appear to be most susceptible at an early age and may die suddenly without premonitory clinical signs.

*Pathology:* Affected animals have classic lesions of Tyzzer's disease including dissemination of bacteria to heart, liver, and/or GI tract with resultant multifocal hemorrhagic necrosis in these locations [105,106].

*Diagnosis:* Unfortunately, antemortem diagnosis is difficult because the organisms do not grow in culture.

*Prevention and control:* Treatment has not been reported but is often unrewarding in other species. Tetracyclines may be attempted.

## Francisella tularensis

*Etiology:* *Francisella tularensis*, the causative agent of tularemia, has been described as both a natural and experimental infection [107–109].

*Clinical signs:* Clinical signs of infection may include lethargy, ataxia, and fever, but animals may also present more acutely or die suddenly. Following experimental aerosol exposure, animals generally succumbed within 1 week of infection.

*Pathology:* At necropsy, animals will have multifocal hepatic necrosis, necrotizing enteritis, bronchopneumonia, lymphadenitis, and splenitis, which are consistent with disease in other species.

*Diagnosis:* In suspected cases, serology may be beneficial to help diagnose the disease but necropsy and histopathology may be beneficial as well.

*Prevention and control:* Limiting contact of free-ranging marmosets to possible hosts such as rodents and other small mammals should limit spread of this disease.

## Leptospira sp.

*Leptospira borgpetersenii* has rarely been reported in Wied's marmosets and presumably could infect common marmosets as well. Expected clinical signs include diarrhea, weight loss, and jaundice, and bloodwork shows hyperbilirubinemia. Diagnosis can be confirmed through serology or at necropsy where animals will have renal and/or hepatic lesions. Leptospiral organisms may be noted with a silver stain or immunohistochemistry [110].

## Other Bacterial Agents

Other potential pathogens include *Yersinia enterocolitica*, which causes miliary hepatic necrosis [53], and

*Burkholderia mallei* (glanders), which induces hepatic necrosis when introduced experimentally [111].

## Parasitic Disease

As in the stomach and intestines, parasitic disease of the liver and gallbladder are rare in marmosets. The most common parasites are *Platynosomum* sp. and *Toxoplasma gondii*. While modern pest control measures and use of antiparasitic agents have reduced the likelihood of transmission by reducing contact with host species, infection is still possible; and one should be familiar with these agents as potential causes of clinical disease.

### Platynosomum sp.

*Etiology:* The trematode flukes *Platynosomum amazonensis*, *Platynosomum marmoseti*, and *Athesmia foxi* may infect callitrichids including common marmosets [61,90,112,113].

*Clinical signs:* These parasites reside in the gallbladder and bile ducts, and clinical signs manifest primarily as weight loss. With a severe infection, one would expect to see hyperbilirubinemia and icterus.

*Pathology:* At necropsy, there is dilation of intrahepatic bile ducts, thickening of the gallbladder, and black discoloration of the bile. Flukes may be grossly visible as small black foreign bodies within the gallbladder or bile ducts. Histologically flukes are associated with portal fibrosis and significant cholestasis.

*Prevention and control:* This parasite can be treated with 60 mg/kg praziquantel, and care should be taken to control cat, snail, lizard, and toad populations, which can all serve as intermediate or paratenic hosts [90].

### Toxoplasma gondii

*Etiology:* *Toxoplasma gondii* has also been reported in callitrichids and other New World monkeys [114–117].

*Clinical Signs:* Experimental infection results in rapid death between 1 and 12 days post infection. Clinically, one would expect to see fever, along with elevations in liver enzymes associated with infection. The organism also commonly infects the kidneys, muscles, heart, lymph nodes, spleen, and lung, which can result in kidney failure, pneumonia, and myocarditis, which may be presenting complaints as well.

*Pathology:* Infection is prominent in the liver where it is associated with multifocal to coalescing inflammation and necrosis, which can be extensive.

*Diagnosis:* Diagnosis may be made from blood smears, though organisms may be present in blood only late in the disease. Due to the acute nature of the disease, treatment in marmosets has not been described but includes trimethoprim–sulfamethoxazole or pyrimethamine + sulfadiazine + leucovorin in other species.

## Viral Diseases

### **Lymphocytic Choriomeningitis Virus**

*Etiology:* Lymphocytic choriomeningitis virus (LCMV) is a member of the family *Arenaviridae*. Disease has been reported in a variety of species, and marmosets are highly susceptible to infection. Originally termed callitrichid hepatitis virus, it was later discovered that this transmissible agent is actually a variant of LCMV [118–121].

*Clinical signs:* Marmosets are most commonly exposed following ingestion of infected rodents, and disease has been associated with the feeding of newborn mice to marmosets [19], though wild mice may also serve as a reservoir [122]. Approximately 1–2 weeks following exposure, animals may present as weak and anorexic, jaundiced, or with unexplained hemorrhage. Sudden death without identification of premonitory clinical signs may also occur. Animals often have elevated liver enzymes.

*Pathology:* The most common and prominent pathologic finding is multifocal hepatic necrosis with Councilman (acidophilic) bodies and mononuclear inflammation. Animals may also have necrosis in the spleen, lymph nodes, adrenal cortex, and intestinal tract.

*Diagnosis:* Diagnosis can be made through serology or, more likely, based on characteristic histopathologic findings and use of immunohistochemistry or other molecular techniques to identify infection.

*Prevention and control:* Care should be taken to avoid infection by controlling the wild rodent population and avoiding the use of mice as food enrichment for marmosets. If disease is suspected, animals should be isolated to avoid spread within the colony, and euthanasia of infected animals and contacts should be considered. Thorough sanitation of the environment is required, and an evaluation of pest control measures should be undertaken to reduce or eliminate the rodent population.

### **GB Virus**

Hepatitis C is a cause of significant morbidity in human populations and is responsible for hundreds of thousands of human deaths annually. Marmosets are susceptible to infection with GB virus B, the most closely related virus to hepatitis C virus, and therefore serve as a useful animal model of hepatitis C [123].

Infected animals develop hepatic pathology similar to that seen in humans with hepatitis C, which include multifocal nonsuppurative hepatitis, formation of lymphocytic nodules, and piecemeal necrosis, which progress to portal fibrosis over the course of approximately 5–6 months. Steatosis may also be present. Progression occurs despite clearance of the virus from plasma [124,125]. These changes are associated with

concomitant changes in plasma insulin and glucagon levels consistent with metabolic dysregulation [126]. While acute experimental infection is not associated with notable clinical signs, one may see an elevation in serum ALT, ALP, and/or LDH clinically.

### **Yellow Fever**

*Etiology:* Marmosets are susceptible to yellow fever, and the virus may occur naturally in wild populations [127–129]. Experimental inoculation of *Callithrix jacchus* may cause disease depending on the specific strain used for infection. In an experiment in which multiple strains were inoculated into common marmosets, the African-origin Asibi strain resulted in low mortality, whereas South American strains such as O.C., J.Z., J.F., Martinez, and A.C. Bolivian strains resulted in high mortality with an average survival time of 5–9 days post infection [79,128].

*Clinical signs:* Clinically one would expect to see weakness, lethargy, and potentially icterus. Depending on the strain, liver enzymes may be elevated and clotting times may be abnormally long.

*Pathology:* Gross pathologic changes are somewhat dependent on strain but generally include icterus, splenomegaly, and congestion or hemorrhage of the stomach. Histologically, there is steatosis and multifocal random hepatic necrosis, which may be associated with intranuclear viral inclusion bodies in hepatocytes. Councilman bodies may also be present.

*Prevention and control:* Unless a facility was importing primates from South America, introduction of this agent into a facility would not be expected. However, as global temperatures rise, the endemic range of mosquitoes harboring this virus (*Aedes aegypti*) could change and lead to an enhanced probability of transmission in some captive settings. As such, measures to control the mosquito population and to limit contact with other infected animals or humans should be implemented to prevent transmission of this virus.

### **Other Viruses**

In addition to these important viruses, marmosets may also be infected experimentally with other pathogens that result in hepatic disease.

Not surprisingly, marmosets are susceptible to *Lassa virus*, the causative agent of Lassa fever. This virus is an arenavirus closely related to LCMV and results in lesions similar to those seen in this important human disease, including hepatocellular necrosis with lesions similar to those described for LCMV above [130].

Marmosets are also experimentally susceptible to Junin virus, the causative agent of Argentine hemorrhagic fever, another arenavirus. Animals present with anorexia, weight loss, and/or neurologic symptoms. Anemia develops over the course of 1–3 weeks, and

leukopenia and thrombocytopenia may also be evident [131,132]. Gross lesions include multifocal hemorrhage in the mouth, pharynx, and esophagus. Histologically, there is multifocal hepatic necrosis along with meningoencephalitis, interstitial pneumonia, and lymphocytic depletion [133].

Marmosets have been used as models to study Marburg virus and Ebola virus. Infection with both results in weight loss, anorexia, fever, and depression. Animals may show hemorrhage from mucosal surfaces and dyspnea. Animals generally succumb to disease within 7–10 days. Pathologic findings are typical of filovirus infection and include hepatocellular necrosis along with a host of other pathologic changes such as splenic necrosis, lymphoid necrosis, and disseminated intravascular coagulation [134–136].

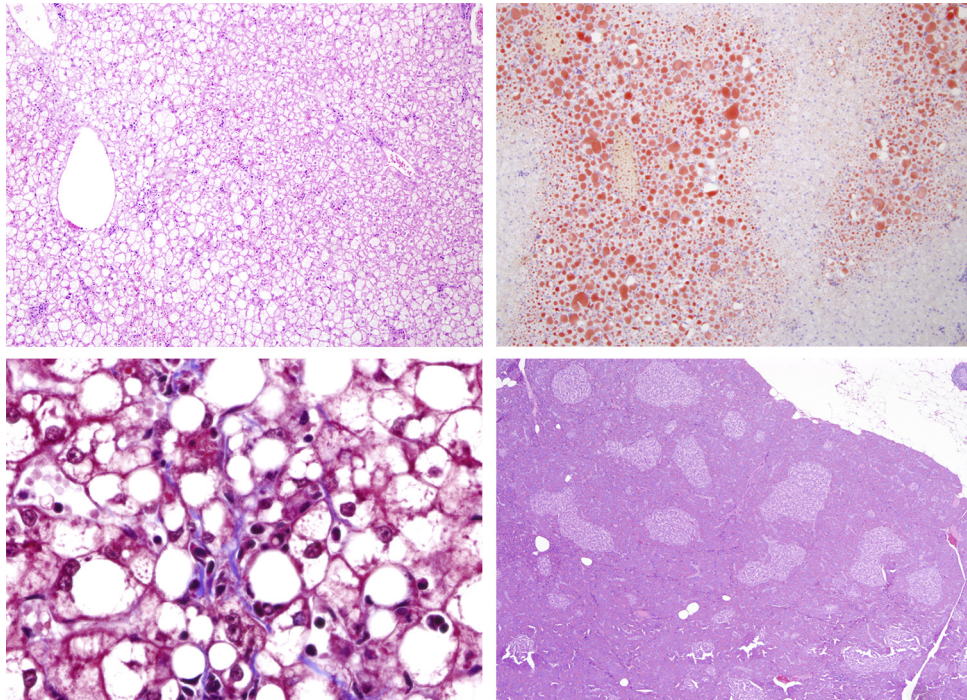
Other species of callitrichids, including several species of *Saguinus*, have been experimentally infected with hepatitis A virus. Animals developed elevated liver enzymes, histopathologic changes in the liver consistent with hepatitis A virus infection, and developed circulating antibody titers. The incubation period was approximately 3–5 weeks [137].

## Noninfectious Diseases

Marmosets commonly develop nonalcoholic fatty liver disease (NAFLD), which sometimes progresses to nonalcoholic steatohepatitis (NASH). In one report, hepatomegaly was present in 18% of marmosets and was identifiable on physical examination and radiographs [138]. NAFLD and NASH are important human diseases, and marmosets may serve as a useful animal model for these conditions.

Marmosets with fatty liver disease are more likely to have high total body weight and body condition scores and are generally more likely to be female than male. Bloodwork findings are reported to include an elevated GGT and triglycerides.

At necropsy, animals will have markedly enlarged livers which, in severe cases, can extend down to the pelvic region. Histologically, there can be both macrovesicular and microvesicular steatosis, which is associated in some cases with inflammation and fibrosis (Fig. 13.6). Management of NAFLD/NASH is not discussed in the literature, but dietary intervention may prove worthwhile (Table 13.1).



**FIGURE 13.6** Marmosets develop fatty liver, which sometimes progresses to nonalcoholic steatohepatitis. Fatty liver is often characterized histologically as macrovesicular steatosis in which hepatocytes contain large, clear, intracytoplasmic fatty inclusions on HE staining (top left). These vacuoles stain with oil red O indicating they are fat (top right). Sometimes, marmosets progress toward nonalcoholic steatohepatitis (NASH), which is characterized by interstitial fibrosis and a ballooning degeneration (Trichrome stain, bottom left). Some of these marmosets also develop diabetes, and histologically animals have large pancreatic islets (bottom right).



**TABLE 13.1** Infectious Etiologies of Multifocal Hepatic Necrosis in the Common Marmoset

Etiology	Key Characteristics
HSV, HVT	Intranuclear inclusion bodies and viral syncytial cells; coalescing regions of hepatocellular necrosis
Lymphocytic choriomeningitis virus	Multifocal hepatic necrosis with Councilman bodies and mononuclear cell inflammation. Lesions in spleen, adrenal cortex, and intestines
GB virus	Multifocal nonsuppurative hepatitis. Piecemeal necrosis, lymphocytic nodules, steatosis
Yellow fever	Steatosis, multifocal random or midzonal necrosis, intranuclear viral inclusion bodies in hepatocytes, and Councilman bodies
<i>Yersinia enterocolitica</i>	Multifocal hepatic abscesses and necrosis. Associated with mesenteric lymphadenitis and ulcerative enterocolitis
<i>Clostridium piliforme</i>	Multifocal hemorrhagic necrosis of liver, heart, and intestine with bacteria at leading edge of necrosis visible using silver stain as long slender rods
<i>Francisella tularensis</i>	Multifocal necrotizing and granulomatous hepatitis along with enteritis, lymphadenitis, and splenitis
<i>Burkholderia mallei</i>	Multifocal microabscesses and necrosis, intralosomal bacilli visible. Also affecting spleen, lung, and nasopharynx with similar histology
Toxoplasmosis	Multifocal necrosis with hemosiderosis with or without PAS + organisms. Also lesions in intestine, heart, lung, kidneys, brain, spleen, and/or lymph nodes

## DISEASES OF THE PANCREAS

### Parasitic Disease

#### *Trichospirura leptostoma*

**Etiology:** Though far less common than it once was, the nematode *Trichospirura leptostoma* causes chronic pancreatitis [139,140].

**Clinical signs:** Infected animals have clinical signs including weight loss, muscle wasting, and anemia. Though not reported, one would expect elevated amylase on serum chemistry. Amylase >800 IU/L should raise the level of suspicion for pancreatitis [141].

**Pathology:** The parasite infects the pancreatic ducts where it is associated with moderate-to-severe ductular fibrosis and blockage of the ducts. Fibrosis expands into exocrine pancreatic tissue.

**Diagnosis:** Parasite eggs can be identified in feces using formalin sedimentation.

**Prevention and control:** Treatment of suspected cases is best accomplished with 50 mg/kg fenbendazole for 14 days. Ivermectin at 200–500 µg/kg may also successfully kill the parasite but is less effective [139].

The German cockroach (*Blattella germanica*) and brown-banded cockroach (*Supella longipalpa*) are intermediate hosts. Initial reports of infection in wild-caught marmosets suggested that this parasite did not cause high morbidity, whereas later reports of laboratory samples indicated a higher incidence of disease. One possible explanation for this dichotomy is that some animals experience a rapid infection due to cockroach infestation, which overloads the body's ability to manage the infection. As such, pest control measures should be implemented to prevent infestation and reduce the risk of transmission to marmoset colonies.

Successfully treated animals may show remarkable weight gain and improvement in clinical signs after treatment. The clinical signs together with marked weight gain post treatment have led some to speculate about this parasite's relationship to MWS [88,89]. While it is clear that the parasite causes wasting and characteristic clinical signs that are readily reversible with treatment, it is unlikely that it is the cause of MWS which, as noted above, is associated with chronic inflammation of the intestines and is still present in colonies despite eradication of this agent.

### Noninfectious Diseases

#### *Diabetes*

Marmosets can develop insulin-resistant diabetes, and this condition is partially dependent on the diet they are fed. Marmosets fed a common, commercially available diet, which has glucose as a main ingredient (32% added glucose), readily develop obesity and prolonged hyperglycemia. Animals fed a high-fat diet also developed hyperglycemia and obesity, though these changes were both less dramatic and delayed by ~6 months [142]. Animals in both groups developed vascular pathology consistent with atherosclerosis and islet hyperplasia consistent with insulin resistance. As noted above, diet is critically important in maintaining healthy marmosets. While palatability is obviously important, the selected diet should be well balanced without unnecessary added sugar.

Animals with insulin resistance or overt diabetes may present with clinical signs including polyuria/polydipsia, anorexia, vomiting, and weakness [143]. Animals may be obese but begin to lose weight as the disease progresses.

Laboratory findings are characteristic of diabetes in other species and include hyperglycemia, hypertriglyceridemia, and glycosuria. Glycosylated hemoglobin (HgbA1c) is also a useful diagnostic tool and is elevated in animals with persistent hyperglycemia. Animals that are euthanized with diabetes will initially show islet hyperplasia at necropsy (Fig. 13.5), but this may progress to islet atrophy as disease progresses.

Dietary management is possible to delay the progression of disease but may prove unrewarding in the long term. Anecdotally, oral hypoglycemic agents such as metformin may be used to treat animals with some success. Insulin therapy could be considered on a case by case basis but is likely not feasible in a research setting due to the intensive care and frequent injections that are required and secondary physiologic changes that would alter the animal's usefulness experimentally.

In addition to developing diabetes naturally, marmosets should also be considered as an animal model for diabetes given the readiness with which they develop insulin resistance and hyperglycemia following a change in diet. Interestingly, marmosets are resistant to diabetes induction with streptozotocin due to altered expression of the GLUT2 glucose transporter in their islets limiting the usefulness of this specific model [144]. However, their islet anatomy and structure are similar to those of humans, making them a potentially useful animal model for an important human disease [145,146].

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