Meeting Report: Spontaneous Lesions and Diseases in Wild, Captive-Bred, and Zoo-Housed Nonhuman Primates and in Nonhuman Primate Species Used in Drug Safety Studies

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Meeting Report: Spontaneous Lesions and Diseases in Wild, Captive-Bred, and Zoo-Housed Nonhuman Primates and in Nonhuman Primate Species Used in Drug Safety Studies


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Abstract

The combination of loss of habitat, human population encroachment, and increased demand of select nonhuman primates for biomedical research has significantly affected populations. There remains a need for knowledge and expertise in understanding background findings as related to the age, source, strain, and disease status of nonhuman primates. In particular, for safety/biomedical studies, a broader understanding and documentation of lesions would help clarify background from drug-related findings. A workshop and a minisymposium on spontaneous lesions and diseases in nonhuman primates were sponsored by the concurrent Annual Meetings of the American College of Veterinary Pathologists and the American Society for Veterinary Clinical Pathology held December 3–4, 2011, in Nashville, Tennessee. The first session had presentations
from Drs Lowenstine and Montali, pathologists with extensive experience in wild and zoo populations of nonhuman primates, which was followed by presentations of 20 unique case reports of rare or newly observed spontaneous lesions in nonhuman primates (see online files for access to digital whole-slide images corresponding to each case report at http://www.scanscope.com/ACVP%20Slide%20Seminars/2011/Primate%20Pathology/view.apml). The minisymposium was composed of 5 nonhuman-primate researchers (Drs Bradley, Cline, Sasseville, Miller, Hutto) who concentrated on background and spontaneous lesions in nonhuman primates used in drug safety studies. Cynomolgus and rhesus macaques were emphasized, with some material presented on common marmosets. Congenital, acquired, inflammatory, and neoplastic changes were highlighted with a focus on clinical, macroscopic, and histopathologic findings that could confound the interpretation of drug safety studies.

Keywords

amyloidosis; Aotus trivirgatus; Armillifer agkistrodontis; Aspergillus fumigatus; Brunner’s gland hyperplasia; bonobo; chimpanzee; Callithrix jacchus; cardiomyopathy; Cebus sp; Cercocebus torquatus torquatus; Cercopithecus nictitans; Chlorocebus aethiops; Chromobacterium violaceum; colitis; Cryptosporidium muris-–like; cytomegalovirus; diabetic nephropathy; encephalitis; enteritis; ependymoblastoma; epitheliotropic lymphoma; gorilla; Gorilla beringei beringei; Helicobacter heliumani-–like; hyperadrenocorticism; intestinal carcinoma; lymphocytic choriomeningitis virus; Macaca fascicularis; Macaca mulatta; Macaca nemestrina; macaque; Mandrillus sphinx; marmoset; metapneumovirus; multiple myeloma; oncocytic adrenocortical carcinoma; orangutan; ovarian teratoma; Pan paniscus; Pan troglodytes; papillomavirus; Papio cynocephalus; pheochromocytoma; Plasmodium inui; pneumonia; Pongo pygmaeus; Saguinus oedipus; simian human immunodeficiency virus; simian immunodeficiency virus; squamous cell carcinoma; tamarin

Session 1 Premeeting Workshop: Drs Lowenstine and Montali

Dr Linda J. Lowenstine, professor of veterinary pathology, microbiology, and immunology, University of California, Davis, provided an overview and comparison of causes of morbidity and mortality of free-ranging and captive-housed great apes and discussed their implication on conservation and management. Dr Lowenstine stated that all the great apes (gorillas, chimpanzees, bonobos, and orangutans) are in peril in their countries of origin from habitat loss, wars, human population encroachment on protected areas, direct predation by humans, and, to a lesser extent, by large carnivores such as lions and leopards. Many of the factors that have decimated apes in the wild are anthropogenic, although natural catastrophes and disease mortality are significant in some populations. Apes that are housed in zoos throughout the world and in sanctuaries in their native lands are affected by some of the same health issues as their wild counterparts, but several problems can be either specific to the captive situation or exacerbated by it. For instance, Dr Lowenstine mentioned that there are geographically restricted infections, such as coccidioidomycosis in gorillas, which is a limiting factor in exhibiting this species in zoos in the southwestern United States, and some parasitic infections that are more common or serious in zoo apes, such as Balamuthia mandrillaris, Strongyloides stercoralis, Balantidium sp, and Enterobius vermicularis. The constellation of diseases affecting wild apes includes many diseases not seen in zoos. For example, Ebola virus has killed hundreds of wild chimpanzees and gorillas. Respiratory

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disease is an important cause of mortality in both wild and captive apes. Outbreaks in wild
habituated chimpanzees and mountain gorillas have recently been associated with human
metapneumovirus and historically with measles. Respiratory syncytial virus is a documented
cause of occasional deaths in chimpanzees and bonobos in zoos. Streptococcus pneumoniae
and Klebsiella pneumonia are seen in both settings. Among zoo apes, respiratory infections
are a more significant cause of mortality in chimpanzees and orangutans than in gorillas.
Bacterial laryngeal air sac infections (Pseudomonas and coliforms) are most common in zoo
orangutans and well documented in rehabilitant semicaptive orangutans in range countries.
Understanding disease affecting great apes in captive and free-ranging populations is
essential to conservation. Pathology is an invaluable tool toward this end, but detailed
postmortem examinations are not always performed, especially in the free-ranging
populations. Long-term behavioral studies provide some useful information, and integration
of postmortem examinations into these studies is becoming more common. Necropsies are
performed most frequently in zoo-housed apes, and in North American zoos, the necropsy
reports are compiled by Species Survival Plan veterinary and pathology advisors into
databases that give a fairly good understanding of the health problems encountered. In free-
ranging apes, a long-term pathology database (1986 to present) exists only for Virunga and
Bwindi Mountain gorillas (Gorilla beringei beringei and G. beringei undecided). There are
some data for common chimpanzees (Pan troglodytes) in the wild, bonobos (Pan paniscus)
in 1 African sanctuary, and “ex-captive rehabilitant” Bornean orangutans (Pongo
pygmaeus). Some of the material presented by Dr Lowenstine has been documented in the
literature.46,66,74,77

Dr Richard J. Montali, from the Johns Hopkins University School of Medicine, provided
an overview of selected infectious diseases of captive New World primates, emphasizing the
Callitrichidae, including marmosets, tamarins, and Goeldi’s monkeys (Callimico goeldii). Dr
Montali focused on callitrichid hepatitis, a syndrome caused by lymphocytic
choriomeningitis virus (LCMV) infection of marmosets and tamarins.44 In captive settings,
LCMV is transmitted to callitrichids by ingestion of rodents, including newborn mice that
carry LCMV. Clinical signs of callitrichid hepatitis include lethargy and icterus with high
mortality. Gross pathology lesions consist of hepatomegaly, splenomegaly, ascites, and both
subcutaneous and internal hemorrhage. In marmosets, histopathology reveals diffuse hepatic
necrosis with acidophilic (Councilman) bodies and inflammation. Lymphoid necrosis in
follicles and mild choriomeningitis also develop. LCMV infection may be confirmed by
immunohistochemistry as well as virus isolation. It is important to recognize LCMV as a
potential zoonotic agent. Dr Montali also reviewed additional viral diseases seen in
callitrichids, including other hepatotropic viruses, such as GBV-B, alpha and gamma
herpesviruses, measles, and encephalomyocarditis viruses. Several common bacterial
diseases have been documented in callitrichids. Streptococcus zooepidemicus septicemia
with suppurative cervical lymphadenitis has been associated with feeding raw horsemeat
to callitrichids. Both Yersinia pseudotuberculosis and Y. enterocolitica can induce severe
suppurative and necrotizing enteritis with serositis, along with abscesses especially
prominent in the liver but also found in spleen and mesenteric lymph nodes. Yersiniosis may
be prevented by controlling carrier avian and rodent species. Callitrichids are also
susceptible to Pasteurella and mycobacterial infections. Parasitic diseases of callitrichids

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include cerebrospinal nematodiasis caused by *Baylisascaris procyonis*, especially in golden-headed lion tamarins (*Leontopithecus chrysomelas*). Spirurids also infect callitrichids. In particular, *Gonglyonema pulchrum*, the tongue worm, induces oropharyngeal lesions after callitrichids ingest infected cockroaches or beetles.

**Session 2 Minisymposium: Drs Bradley, Cline, Sasseville, Miller, Hutto**

**Dr Alyys Bradley**, director of pathology, Charles River Laboratories Preclinical Services, Europe, reviewed the incidences and range of spontaneous findings in cynomolgus macaques (*Macaca fascicularis*) in toxicity studies. Differentiating drug-induced changes from spontaneous findings is challenging due to the limited numbers of animals used per sex, per group, and up-to-date historical control data in purpose-bred nonhuman primates (NHPs) are not readily available. Dr Bradley reviewed recent data collected from control animals (12–30 months of age; body weights, 1.6–2.5 kg) that were sham dosed with appropriate vehicle and euthanasia performed by intravenous sodium pentobarbitone and exsanguination. The majority were from Bioculture, Mauritius (95%), as well as Guanxi Grandforest Primate Company, China. Dr Bradley mentioned that the most common findings were inflammatory cell infiltrates in liver, kidney, heart, salivary glands, and stomach (listed in order from highest to lowest incidence) and ectopic tissues (eg, thyroid). All major organ systems were discussed in detail to include congenital lesions, degenerative, traumatic, iatrogenic, and proliferative lesions, as well as commonly encountered infectious agents. Much of this the work is reported in a review by Chamanza et al.12

**Dr Mark Cline**, professor of pathology/comparative medicine at Wake Forest School of Medicine, reviewed normal findings and selected common urogenital lesions found in cynomolgus macaques (*M. fascicularis*). The urogenital system of NHPs is similar to that of human primates, and this similarity is the basis for much of their use in toxicologic pathology. Dr Cline focused on those lesions that are most common or most likely to confound the interpretation of toxicologic findings in the urogenital tract. The greatest complexity and difficulty in interpretation is often found in the female reproductive system, and Dr Cline discussed aspects of normal physiology as well as common pathologic findings. Of particular interest is the occurrence of papillomavirus (PV), which may occur as a clinically silent and enzootic infection of cynomolgus macaque colonies. Infections with PV are common in female macaques of breeding age and produce cervical intraepithelial neoplasms that may confound the interpretation of drug-related changes.80 Screening has identified a background genital PV prevalence as high as 35% in colony-acquired adult female cynomolgus macaques,80 a prevalence similar to that for human PV infection in sexually active younger women. Lesions are most common in the transformation zone.79 Recent genetic work has detected 12 different viruses in cynomolgus macaques.15

**Dr Vito Sasseville**, Executive Director in Preclinical Safety: Discovery and Investigative Safety, Novartis Institutes for Biomedical Research, discussed background and spontaneous changes in the gastrointestinal tract of NHPs in drug safety studies. He noted that subacute to chronic gastritis was one of the most common findings in cynomolgus macaques, whereas chronic lymphocytic enteritis (wasting marmoset syndrome) was most common in common marmosets (*Callithrix jacchus*). Other, less common sporadic background findings in
macaques, such as acute gastric dilatation, gastric muscularis degeneration, ectopic pancreas, hyalinized chief cells, and parasitic granulomas, were briefly discussed. Because background inflammatory changes can be associated with commensal pathogens, an overview of primary and opportunistic pathogens of the gastrointestinal tract that could have an impact on the interpretation of drug safety studies was discussed. The discussion covered common primary bacterial pathogens such as *Campylobacter* spp, *Shigella* spp, *Yersinia* spp, *Helicobacter* spp, and *Clostridium difficile* and opportunistic pathogens including *Mycobacterium avium* complex, *Rhodococcus* spp, *enteropathic E. coli*, and *C. piliforme*. Lymphocryptovirus-induced gastrointestinal lymphomas and squamous epithelial proliferative changes, rhesus rhadinovirus-associated retroperitoneal fibromatosis, cytomegalovirus, and adenoviral disease were covered. Last, Dr Sasseville gave an overview of primary parasitic pathogens, such as *Strongyloides stercoralis/S. Fullerborni* (Old World primates), *S. cebus* (New World primates), *Trichuris trichiura* (macaques), *Giardia intestinalis* (common marmosets), and common opportunistic parasites in macaques, such as *Enterocytozoan bieneusi* and *Cryptosporidium parvum*. Much of the information presented has been covered in various reviews.12,22,31,38,52,53

Dr Andrew Miller, from the Department of Comparative Pathology, New England Primate Research Center, Harvard Medical School, reviewed the important aging pathologies of the rhesus macaque (*M. mulatta*) with special emphasis on cardiac, central nervous system, and renal pathology, amyloidosis, and spontaneous neoplasia. Rhesus macaques can be found throughout the Indian subcontinent and China. The majority of rhesus macaques currently in the United States are either imported from China or are born and raised in the United States in dedicated breeding facilities, with the average lifespan of 25 to 30 years.38,67 Dr Miller reviewed some of the differences related to geographic origin of rhesus macaques that may affect disease development and manifestation. Spontaneous cardiac lesions are one of the more common findings in aged rhesus macaques, with myocardial fibrosis of unknown etiology being the most common finding. Atherosclerosis is not a naturally occurring disease in rhesus macaques but can be induced by dietary manipulation (ie, a Western diet). Arteriosclerosis is uncommon but does occur spontaneously in rhesus macaques. A spectrum of “normal” histologic findings can be found in the brain of aged rhesus macaques, including vascular mineralization, iron deposits in the Virchow-Robin space, lipofuscin accumulation in neurons, corpora amylacea, amyloid deposits, spheroids, neuronal degeneration, satelitosis, gliosis, and white matter vacuolation. In the kidney, some degree of chronic glomerulonephritis is very common in rhesus macaques with advancing age, although the majority of animals with glomerulonephritis fail to show consistent clinical signs. Several important, nonspecific findings that are common in rhesus macaques include multinucleated epithelial cells lining the collecting ducts in the kidney and hyaline intracytoplasmic inclusion bodies in transitional epithelium of the renal pelvis, ureters, and bladder. Other, nonspecific, age-associated findings in the hearts of rhesus macaques include nuclear heterogeneity with impressive variations in nuclear size and shape and multifocal, mild aggregates of lymphocytes scattered throughout the myocardium. Dr Miller discussed that the 2 most important forms of amyloidosis encountered in aging rhesus macaques are AA amyloidosis and islet amyloidosis. Systemic AA amyloidosis is common in rhesus macaques with amyloid deposits primarily in the small intestine; however, deposition in the
large intestine, spleen, liver, adrenal gland, and mesenteric lymph nodes is common.\textsuperscript{40} Amyloidosis in the macaque is generally thought of as a sequela to chronic inflammation and is seen commonly in animals with chronic enterocolitis or arthritis.\textsuperscript{40} Islet amyloidosis derives from the extracellular deposition of amylin (islet amyloid polypeptide) and correlates strongly with type II diabetes mellitus and insulin resistance. Up to one-fourth of rhesus macaques in captivity can develop some degree of insulin resistance and islet amyloidosis by 20 to 25 years of age. Last, spontaneous neoplasms in rhesus macaques are being identified more frequently as many colonies now maintain aging animals.\textsuperscript{38,56} The majority of recorded neoplasms are benign, often incidental findings at necropsy. By far, the most common malignant neoplasm of the rhesus macaque is large intestinal carcinoma, frequently at the ileocecal junction, although they can be found in the colon as well. Regional and distant metastasis (including carcinomatosis) occurs late in the disease progression.\textsuperscript{59} Other common neoplasms include leiomyomas in the uterus, ovarian granulosa cell tumors, bronchioloalveolar adenomas, and transitional cell hyperplasia/adenoma of the renal pelvis. Benign skin tumors including lipomas, sebaceous adenomas, hemangiomas, and follicular tumors are fairly commonly and usually clinically insignificant.

**Dr David Hutto**, senior director, Drug Safety at Eisai, Inc, discussed the impact of plasmodium infection in NHPs on drug development. South Asian macaques can be infected with several species of *Plasmodium*, depending on the presence of appropriate vectors and supporting vector habitat.\textsuperscript{18,28,64} The prevalence of infection in macaques from these malaria endemic regions range from 10\% to 70\%. The plasmodial life cycle is complex, involving 2 hosts, mosquito and primate, and 2 target tissues in primates, liver and blood. Natural and persistent infection of macaques by *Plasmodium spp* is generally relatively benign. If there is recrudescence leading to a high level of parasitemia, anemia from the effects of the intraerythrocytic stages of the disease may ensue. Macaques imported from Asia should be assumed to be infected with *Plasmodium*. Plasmodial recrudescence and disease during the course of drug safety studies may (1) indicate recrudescence by the drug or other variable, (2) make study results difficult to interpret, or (3) nullify the results from the study. Diagnostic tests for plasmodial infection exist but may be insensitive or impractical. Antiplasmodial treatment is generally thought to be effective and safe. Therefore, drug development scientists and staff in vivaria often face the dilemma of how to handle NHPs that are presumed to be infected with a hemoparasite that may cause disease or obfuscate interpretation of study results. Options include (1) test and stratify animals to treatment groups by results, (2) test and treat positive animals, (3) treat all animals without testing, or (4) test or treat no animals. The approaches each have different consequences to consider.

**Case Reports**

Twenty case reports were presented that included some rare or newly observed pathogens and/or lesions in various species of NHPs. Brief case histories, morphologic diagnosis, etiology (when applicable), and short discussions are listed below. All cases were digitally scanned (20× objective). For digital whole slide images corresponding to each case report, see supplemental files at [http://www.scanscope.com/ACVP%20Slide%20Seminars/2011/](http://www.scanscope.com/ACVP%20Slide%20Seminars/2011/)
This supplement will serve as a unique resource for training and continuing education in primate pathology.

**Case 1: Claudine Tremblay (Charles River Laboratories)**

**History**—An 8-year-old orchiectomized male cynomolgus macaque (*M. fascicularis*; Bioculture LTD, Mauritius Island) administered control article was found dead on study day No. 67.

**Morphologic diagnosis:** Right ventricle: degenerative and/or necrotizing cardiomyopathy, extensive, marked; myocarditis, chronic, multifocal, moderate.

**Etiology:** Unknown.

**Discussion:** Spontaneous lesions of the cardiovascular system are known to occur with NHPs used in nonclinical safety testing. The degenerative and/or necrotic changes in this case extended from the base of the heart to the apex of the right ventricle and inward from the pericardium to approximately two-thirds thickness of the right ventricle generally sparing the endocardial region and papillary muscles. This case represents an unusually severe spontaneous cardiac lesion that led to unexpected death in a cynomolgus macaque.13,34,72

**Case 2: Karen Terio (University of Illinois, Zoological Pathology Program)**

**History**—A 9-year-old male chimpanzee (*P. troglodytes*) housed at the current facility for 5 years was 1 of 7 chimpanzees with reduced activity, appetite, and signs of respiratory disease (tussis and clear to opaque nasal discharge). Despite medical intervention, the animal became cyanotic, dyspneic, and dorsally recumbent and died within 24 hours. The other affected chimpanzees received supportive care and survived.

**Morphologic diagnosis:** Lung: necrotizing bronhointerstitial pneumonia, rare intralesional gram-positive cocci and coccobacilli, subacute, marked.

**Etiology:** Human metapneumovirus (hMPV) confirmed by polymerase chain reaction amplification from lung.

**Discussion:** Human metapneumovirus, a member of the Paramyxoviridae, was discovered in 2001 as a cause of respiratory disease in young children.70 In humans, disease varies in severity from mild self-limiting illness to severe respiratory failure requiring ventilation. In NHPs, experimental infection of cynomolgus macaques with hMPV resulted in mild erosive lesions in airways with loss of cilia and erosive bronchitis and bronchiolitis.32 Respiratory disease outbreaks in habituated free-ranging chimpanzees at Mahale Mountains National Park in Tanzania and in free-ranging mountain gorillas (*G. beringei beringei*) have been associated with metapneumovirus infection.32,49 The source of infection in this chimpanzee case was not determined, but infection was presumed to be anthropozoonotic.
Case 3: Kerstin Mätz-Rensing (German Primate Center)

**History**—An adult male cynomolgus macaque (*M. fascicularis*) serving as a control animal on a study. This animals had no overt clinical symptoms or signs of disease, and all laboratory parameters were within the normal ranges.

**Morphologic diagnosis:** Lung: systemic pentastomiasis with mild inflammatory reaction.

**Etiology:** *Armillifer agkistrodontis.*

**Discussion:** Visceral pentastomiasis is an unusual parasitic zoonosis caused by larval stages of several pentastome species, parasites that form a unique phylum with characteristics of arthropods and annelids.\(^6\) Today, pentastomes are regarded as a group of modified parasitic crustaceans probably related to branchiurans within the family of anthropods. Like humans, NHPs accidentally serve as intermediate hosts, which acquire infections by ingestion of eggs passed in the feces or nasal secretions of the definitive hosts, usually snakes.\(^6\) Most reported cases have occurred in the tropics and subtropics, but the incidence in the Northern hemisphere might be increasing due to international tourism and trade. In this case, as well as in most other cases, neither clinical symptoms nor noteworthy inflammatory tissue reactions were observed, despite abundant parasites. Massive nymphal burdens as in this case may result from ingestion of intact, gravid female parasites shed from the nares and mouths of infected snakes. Large burdens of pentastome nymphs suggest that the infected animal must have eaten numerous infective larvae at one time or ingested a snake with numerous pentastome adults or consumed infected prey repeatedly over a longer period. Pentosome nymphs usually are identified as an incidental finding during radiology, ultrasound, surgery, or necropsy and should be considered as a differential diagnosis for visceral cysts in animals originating from habitats with typical snake hosts.

Case 4: Eva Gruber-Dujardin (German Primate Center)

**History**—An 18-year-old putty-nosed monkey (*Cercopithecus nictitans*) resident in a zoo collection since 2007. After a fight among group members, the animal showed apathy, tachypnea, and vomiting. Examination revealed a perforating wound on the right lateral thorax and unilateral pyothorax. Clinical chemistry showed elevated alkaline phosphatase, glutamate pyruvate transaminase, cholesterol, glucose, and cortisol. Despite medical intervention, the animal’s condition deteriorated, and it developed neurological signs 10 days after treatment and was euthanized.

**Morphologic diagnosis:** Lung: pleuropneumonia, necrotizing, suppurative, acute, multifocal, marked, with Splendore Hoeppli phenomenon, and numerous intralesional fungal hyphae consistent with *Aspergillus fumigatus* (1). Cerebral cortex: meningoencephalitis, necrotizing, suppurative, acute, multifocal, marked with multifocal thrombosis, necro suppurrative vasculitis, and numerous intralesional fungal hyphae consistent with *A. fumigatus* (1); right adrenal gland: oncocytic adrenocortical carcinoma (2)

**Etiology:** *A. fumigatus* (1); unknown (2).
Discussion: Oncocytic adrenocortical neoplasms are rare in humans and have never been described in NHPs.\textsuperscript{2,8,75} They have distinctive morphologic features that include eosinophilic granular cytoplasm containing numerous mitochondria. The majority of oncocytic adrenocortical neoplasms described in humans are benign with only 18 oncocytic adrenocortical carcinomas reported in the literature.\textsuperscript{2,8,75} Moreover, oncocytic adrenocortical neoplasms in general are almost always nonfunctional (ie, hormonally inactive) with only one reported case of a functional oncocytic adrenocortical neoplasm that was associated with clinical signs of Cushing’s syndrome.\textsuperscript{2} The oncocytic adrenocortical neoplasm in this case was associated with clinical, laboratory, and pathologic findings of hyperadrenocorticism or Cushing’s syndrome, including high blood cortisol levels, increased liver enzymes, mild to moderate hepatic lipidosis, truncal obesity, long-term infertility, and alopecia with associated atrophic skin changes microscopically. Immunosuppression is another feature of hyperadrenocorticism and consistent with invasive aspergillosis and generalized lymphoid atrophy noted on histology in this case.

Case 5: Martha A. Delaney (University of Illinois, Zoological Pathology Program)

History—A 17-year-old captive-born male red-capped mangabey (Cercocebus torquatus torquatus) had been housed with other mangabeys (red-capped [Cercocebus torquatus] and sooty [C. atys]), Colobus monkeys, and Mandrills in a zoo collection. The animal had a 7-year history of episodic vomiting, regurgitation, inappetance, and weight loss with surgical excision of a gastric mass approximately 1 year prior. Despite medical intervention, the animal’s condition declined, and euthanasia was elected. The animal was positive for simian immunodeficiency virus (SIV), Ebstein-Barr virus, foamy virus, simian agent 6, and negative for simian retrovirus, and simian T-lymphotropic virus.

Morphologic diagnosis: Small intestine and colon: enterocolitis, granulomatous, multifocal to coalescing, mild to severe, with multinucleated giant cells and lymphoid hyperplasia-disseminated giant cell disease.

Etiology: SIVsmm.

Discussion: This captive-born red-capped mangabey had lesions consistent with disseminated giant cell disease affecting the entire gastrointestinal tract in varying severity. SIV-positive macrophages and multinucleated giant cells were identified in affected regions by immunohistochemistry with anti-SIV antibodies and confirmed by in situ hybridization. Red-capped mangabeys are known to harbor SIVrcm without developing disease similar to multiple African NHP species that have host-adapted SIV strains.\textsuperscript{1,6,60} However, preliminary data suggest that this animal was infected with SIVsmm rather than SIVrcm. Confirmation of this finding is important because this case may represent an unusual cross-species SIV transmission event leading to disease in an African NHP species. Additionally, lymphoproliferative disease was noted in lymphoid organs (spleen, bone marrow, and lymph nodes) and extranodal organs (kidney, testis, esophagus, and salivary gland). Lymphocytes in these sections were admixed B and T cells based on immunostaining for CD3 and CD79a markers. These regions also contained few scattered multinucleated giant cells. Disseminated giant cell disease and lymphoproliferative disease have been recognized as
SIV-induced lesions in macaques. While giant cell disease has also been reported in sooty mangabeys infected with SIVsmm, reports of disease associated with SIV infections in the natural host are rare. Additionally, documented SIV-induced lesions in naturally infected red-capped mangabeys are lacking. Because of their different life histories and management in captivity, zoo-housed NHPs can contribute to the understanding of the pathogenic potential of SIV in various species.

**Case 6: Lisa Schmidt (Wake Forest University School of Medicine)**

**History**—A 22-year-old female African green monkey (*Chlorocebus aethiops*), acquired from another research facility approximately 4 years prior, presented with elevated globulin (8.1 g/dl) and increased total protein (10.4 g/dl) levels. During a follow-up exam 3 months later, the total protein and globulin levels remained elevated, and a serum protein electrophoresis showed an increase in the beta region. The animal was asymptomatic, and serum globulin and protein levels remained elevated until approximately 9 months later, when it presented with increased upper respiratory sounds, a swollen lower right eyelid, and ocular and nasal discharges. A computed tomography scan showed a large mass in the right ophthalmic orbit, which was associated with bony lysis of the zygomatic bone.

**Morphologic diagnosis:** Thoracic vertebra: bone marrow, multiple myeloma; articular processes: osteoarthritis, chronic, multifocal.

**Etiology:** Unknown.

**Discussion:** Neoplastic plasma cell infiltrates were present in the zygomatic bone, mandible, maxilla, dorsal lamina of the thoracic vertebra (the slide chosen as an unknown for the workshop), palatal, and frontal and parietal bones. Osteolysis was only seen radiographically in the zygomatic bone. Multiple myelomas are neoplasms of plasma cell origin with multifocal involvement of bone marrow or skeleton. Typically, multiple myelomas result in an overproduction of light and heavy chain monoclonal immunoglobulins, which can be found in the serum and/or urine of people and animals with multiple myeloma. This animal had asymptomatic monoclonal hyperglobulinemia approximately 2 years prior to presentation, which is consistent with monoclonal gammopathy of unknown significance (MGUS) or smoldering (asymptomatic) multiple myeloma (SMM). In humans, multiple factors, including MGUS or SMM, are considered risk factors for developing multiple myeloma. Approximately 39% of patients with MGUS and 75% of patients with SMM develop multiple myeloma. In this animal’s case, severe chronic dental disease may have provided the chronic antigenic stimulation that is considered a predisposing cause of myeloma in humans. Vertebral osteoarthritis is considered an incidental, age-related finding in this African green monkey.

**Case 7: David Liu (Tulane University, Tulane National Primate Research Center)**

**History**—A 10-year-old Indian rhesus macaque (*M. mulatta*) was presented for multiple pinpoint hemorrhages on the ventral midline and an open wound on the left inner thigh. The animal died 1 week after treatment.
**Morphologic diagnosis:** Lung: abscesses, thrombosis, vasculitis, pleuritis, and intralesional bacillus-shaped bacteria, multifocal, severe.

**Etiology:** *Chromobacterium violaceum.*

**Discussion:** *Chromobacterium violaceum* is a gram-negative saprophytic bacterium of soil and water in tropical and subtropical regions of the world. Although infections of humans and animals are rare, the outcomes are often fatal due to rapid septicemia with multiple abscesses, predominantly in lung, liver, and spleen. In the United States, chromobacteriosis has been mostly reported from the southeastern states, such as Florida, Louisiana, and Texas. Patients with neutrophil dysfunction in chronic granulomatous disease or severe leukocyte glucose-6-phosphate dehydrogenase deficiency have higher susceptibility to chromobacterial infections. Septicemia in patients with low CD4 T cells is further evidence suggesting that an immunocompromised immune system may be involved in chromobacteriosis. *C. violaceum* also produces hemolysins, colicins, and detoxification enzymes that block destruction by host defense systems.

**Case 8: Judit Markovits (Novartis Institutes of Biomedical Research)**

**History:** This 3-year-old intact female cynomolgus macaque (*M. fascicularis*) was born in China (Grand Forest Trading) and was transferred to a quarantine facility in the United States for 6 months. Subsequently, she was transferred to a research facility 3 months prior to being placed on a short-term safety study. There were no clinical or gross findings.

**Morphologic diagnosis:** Stomach, fundus: protozoa, schizonts, male gamonts, and oocysts, approximately 3–8 µm in diameter, diffuse, moderate (1); bacteria, spiral-shaped, diffuse, minimal (2).

**Etiology:** *Cryptosporidium muris*-like protozoa (1); *Helicobacter heilmannii*-like (2).

**Discussion:** This is the first recognized case in our laboratory of a *C. muris*-like infection in the stomach of an immune-competent cynomolgus macaque. The organisms were not identified in other animals. Clinical presentation and histologic features of this case were similar to the cluster of cases published in immunosuppressed cynomolgus macaques, including the unknown source of infection. Numerous protozoa, 3–8 µm in diameter, representing various stages of development, including trophozoites and immature and mature schizonts, were located in microvillus border of glandular epithelium in the gastric fundus primarily localized to upper portion of glands. The cardia and pyloric antrum were free of the organism. Epithelial cells of parasitized glands contained an increased amount of pale staining mucus, but there was no evidence of cellular degeneration or an inflammatory reaction. Electron microscopy showed that parasites were located in parasitophorous vacuoles and attached to host cells with a prominent feeder organelle similar to that described for *C. muris*, which parasitizes gastric glands of rodents. Polymerase chain reaction and sequencing showed that this organism clustered with *C. muris* and *C. andersoni*. As a differential diagnosis, trichomoniasis could be considered (especially in immune compromised animals), although those organisms are typically tear shaped and larger (3–35 µm in diameter). Additionally, fundic glands occasionally contained *H.*
heilmannii–like spiral bacteria, a common incidental finding in macaques.22 Gastric cryptosporidiosis in cattle is now considered to be produced by \textit{C. andersoni} and may be associated with inflammatory and epithelial changes causing decreased production in feedlot animals.8 Mice experimentally infected with \textit{C. muris} and \textit{H. felis} had more severe lesions than those not having coinfections.63

\textbf{Case 9: Michael Owston (Texas Biomedical Research Institute, Southwest National Primate Research Center)}

\textit{History:} A 16-year-old female baboon (\textit{Papio cynocephalus}) with multiple sex skin traumas over several years and recent nonhealing wound/dermatitis of sex skin.

\textit{Morphologic diagnosis:} Skin: neoplasia, squamous cell carcinoma, infiltrative (1); amoebic dermatitis (2).

\textit{Etiology:} Unknown (1); protozoa, amoeba, 20–30 µm in diameter (2).

\textit{Discussion:} Squamous cell carcinoma (SCC) is an infrequent neoplasm in baboons, composing \% of all neoplasms.16,17,26 Squamous cell carcinoma often occurs in the perineum/sex skin and adjacent tissues of baboons; another common location of SCC is the oral cavity, and less commonly other areas of the skin are affected. Squamous cell carcinoma was twice as common in females as males, and all reported perineal lesions were in females.16,17,26 Squamous cell carcinoma often presents as a chronic, nonhealing wound of the sex skin and is frequently initially diagnosed as trauma, which is common on the sex skin, leading to prolonged and ineffective therapy. Another differential diagnosis of nonhealing lesions of the sex skin in baboons is African histoplasmosis (\textit{Histoplasma capsulatum} var. Duboisii), which can be easily diagnosed on impression smears. Squamous cell carcinoma in baboons frequently metastasizes to lymph nodes. Squamous cell carcinoma has been associated in humans and NHPs with chronic irritation, sun exposure, and PV infection. Chronic irritation from trauma and sun exposure are likely contributors to SCC in baboons, but PV has not been identified in baboon SCC. However, baboons do get perineal infection with herpes papio virus 2, which could be involved in the development of the lesions.

The additional, incidental finding of amoebae invading the ulcerated tissues is unusual. Several species of amoebae can infect NHPs, including \textit{Acanthamoeba}, \textit{Balamuthia}, and \textit{Naegleria}, but skin infection is not the most common presentation.73 Intestinal/fecal amoebae, such as \textit{Entamoeba}, are common but are generally nonpathogenic. Persistent moisture of the perineum and fecal contamination may have predisposed to this opportunistic infection.

\textbf{Case 10: Carole Harbison (Harvard Medical School, New England Primate Research Center)}

\textit{History:} An 8-year-old colony-born rhesus macaque (\textit{M. mulatta}) that received multiple inoculations of SIV with no significant clinical problems noted prior to euthanasia for study purposes.
**Morphologic diagnosis:** Left ovary: teratoma.

**Etiology:** Unknown.

**Discussion:** Teratomas, also known as dermoid cysts, are generally benign tumors that contain various well-differentiated tissues derived from neoplastic primordial germ cells. The most common presentation is as a single unilateral ovarian mass, though they can occur bilateral or multifocal. Neoplastic tissues are composed of a combination of disorganized tissue elements from 2 or more embryonic germinal layers (ectoderm, mesoderm, and endoderm) that differentiate into any tissue, including lymphoid or nervous tissue, fat, skin, or glandular epithelium, and they often include distinctive structures such as mineralized teeth or bone, cartilage, and hair. The tumor may be solid, or portions of the mass derived from gastrointestinal or epidermal tissue may become cystic. Teratomas are rare in most animal species but are relatively common in humans, accounting for up to 30% of ovarian tumors. Teratomas of the ovary in rhesus macaques are relatively common and usually incidental findings on necropsy. \(^{41,51}\) The histologic appearance varies based on the composition of the contributing tissues and degree of differentiation. Teratomas can be differentiated from the other germ cell tumors of the gonad, dysgerminoma in females and seminoma in males, as those tumors retain their primordial germ cell appearance without differentiation into tissues from 2 or more germinal layers.

**Case 11: Shiva Shanmukhappa (Harvard Medical School, New England Primate Research Center)**

**History**—An 18-year-old female mandrill (*Mandrillus sphinx*). Two months prior to necropsy, hypoproteinemia and hypoalbuminemia were noted. Peripheral edema developed 5 days after the first reports of decreased appetite. Chemistry panel showed moderate hypoproteinemia, marked hypoalbuminemia, mild increase in globulins, and mild azotemia. The animal died spontaneously.

**Morphologic diagnosis**—Liver and blood vessels: amyloidosis, diffuse, severe.

**Etiology**—Serum amyloid A (SAA) protein.

**Discussion**—AA or reactive “secondary” amyloidosis is the most clinically relevant systemic amyloid-associated disease found in humans and NHPs, and it results from the pathologic deposition of an approximately 76-residue N-terminal fragment of the SAA protein. \(^{27}\) This precursor molecule is an acute-phase apolipoprotein synthesized mainly by hepatocytes under control of interleukins 1 and 6, as well as TNFα. \(^{27}\) In humans, the plasma concentration of SAA normally is approximately 0.1 mg/ml but can increase over 1000-fold in response to an inflammatory stimulus. As part of this process, the SAA molecule undergoes partial proteolysis, and the N-terminal cleavage product is deposited systemically as amyloid fibrils in vital organs, including the liver, spleen, kidneys, and adrenal glands. With rare exceptions, AA amyloidosis develops in patients with chronic inflammatory or infectious diseases (chronic synovitis, tuberculosis, gastroenteritis) or other conditions that are associated with sustained elevation of SAA levels (eg, certain forms of cancer,
Castleman disease, and familial Mediterranean fever.\textsuperscript{27} AA-related amyloid also has been found in cats, sheep, goats, cattle, dogs, horses, rabbits, hamsters, and birds, as well as in primates such as rhesus and pigtailed macaques, chimpanzees, and common marmosets.\textsuperscript{21,39} In cases of systemic amyloidosis in NHPs, organs that commonly have amyloid deposition include the liver, adrenal gland (at corticomedullary junction), small intestine, lymph nodes, and spleen. Renal amyloidosis is an uncommon presentation of systemic amyloidosis in NHPs. The current case was especially interesting, as there was systemic amyloid deposition in all the above organs in addition to the salivary gland and the urinary bladder.

**Case 12: Andrew Miller (Harvard Medical School, New England Primate Research Center)**

**History:** A 13-year-old female common marmoset (*Callithrix jacchus*) euthanized due to wasting and poor body condition.

**Morphologic diagnosis:** Small intestine: carcinoma with signet ring cell formation, multifocal.

**Etiology:** Unknown.

**Discussion:** Small intestinal adenocarcinomas are the most common gastrointestinal tumor in common marmosets.\textsuperscript{42} They have a predilection for the proximal jejunal-duodenal junction, although rare reports of carcinomas exist in other parts of the small intestine. Grossly, these typically appear as focal strictures, and although not grossly apparent, metastases to regional lymph nodes are often found histologically. Animals that develop this neoplasm are typically around 6 years of age, and there is no sex predilection. Often, the neoplasms are found as incidental findings during routine necropsy surveillance. No known etiologic agent exists that is associated with the development of the neoplasm.

**Case 13: Saravanan Kaliyaperumal (Harvard Medical School, New England Primate Research Center)**

**History:** An adult male Capuchin monkey (*Cebus sp*) that was in failing health and was a suspect type II diabetic.

**Morphologic diagnosis:** Spleen: lymphoma (T cell).

**Etiology:** Unknown.

**Discussion:** Currently, there are no reports of lymphoma in capuchin monkeys. The majority of lymphomas in NHPs involve viral infection. These include rhesus lymphocryptovirus-induced lymphoma in rhesus macaques and *Herpesvirus saimiri*–induced lymphoma in common marmosets.\textsuperscript{11} Although no viral cause of lymphoma in this capuchin monkey was detected, a viral cause is highly likely. Because the majority of NHP lymphomas are B cell in origin, the T-cell origin in this current case is more unusual. Lymphoma in humans and NHPs (especially baboons) are associated with viruses related to the human T-causative agent of adult T-cell leukemia/lymphoma (ATL).\textsuperscript{81} Although no
reports exist of simian T-cell leukemia-associated lymphoma in New World primates, a virus similar to it could be involved in the development of lymphoma in the current case.

**Case 14: Basel Assaf (Harvard Medical School, New England Primate Research Center)**

**History**—A 5 year-old, male, intact, common marmoset (*C. jacchus*) on an experimental carbohydrate-rich diet protocol to study the effects of dietary changes on development diabetic retinopathy. Significantly increased HbA1c and fasting blood glucose levels confirmed hyperglycemia in this animal.

**Morphologic diagnosis:** Kidney: interstitial nephritis and mesangioproliferative glomerulonephritis with tubular proteinosis, chronic, diffuse, severe.

**Etiology:** Experimentally induced diabetes mellitus.

**Discussion:** Chronic, age-associated nephropathy is commonly observed in callitrichids (marmosets and tamarins). Clinically, the disease is usually associated with signs of nephrotic syndrome. Typical histopathologic findings are characterized by mesangial proliferation, proliferation and sclerosis of Bowman’s capsule, glomerular sclerosis and obsolescence, tubular degeneration and proteinosis, interstitial fibrosis, and interstitial mononuclear cell infiltration.

Chronic progressive (old rat) nephropathy is a multifactorial condition commonly seen in old male Sprague-Dawley and Fischer 344 rats that has been associated with mesangial deposition of IgM. In humans, IgM nephropathy is strongly associated with deposition of IgM and components of the complement system in the mesangium, indicating activation of the classical complement pathway. While IgM has been similarly detected in the kidneys of adult marmosets, it is not a consistent finding. Additionally, IgM deposition does not always correlate with the age of the animal, and deposits have been observed in a 24-day-old marmoset. Other evidence has implicated IgA developed against gliadin, a dietary wheat protein in the pathogenesis of wasting marmoset syndrome and immune-complex glomerulopathy in marmosets, with striking similarities to IgA-nephropathy/Berger’s disease in humans. Although the histomorphology of this entity closely resembles old rat nephropathy and human IgA or IgM nephropathies, the age of this animal, experimental manipulation, and clinical history favor the final diagnosis of diabetic nephropathy. Diabetic nephropathy is the most common cause of end-stage renal failure in the United States. Diabetic nephropathy is a multifactorial progressive kidney disease resulting from alterations in hemodynamic and fibrotic cytokines, such as transforming growth factor β1 and angiotensin II, respectively, leading to angiopathy of capillaries in the kidney glomeruli, diffuse glomerulosclerosis, and nephrotic syndrome. Consistent with the final diagnosis of diabetes, co-morbid histologic findings included steatohepatitis, coronary atherosclerosis, and diabetic retinopathy. Another 3 animals were similarly fed carbohydrate-rich diet and developed the same spectrum of diabetic changes.
Case 15: Lisa Kattenhorn (Harvard Medical School, New England Primate Research Center)

**History**—Adult, male owl monkey (*Aotus trivirgatus*) with anemia and a mass over the right humerus. The animal appeared bright, alert, and responsive; however, due to a combination of factors, such as advanced age, poor body condition, and anemia, this animal was given a poor prognosis and euthanized.

**Morphologic diagnosis:** Small intestine (jejunum): epitheliotropic lymphoma.

**Etiology:** Unknown.

**Discussion:** To our knowledge, this is the first documented case of intestinal epitheliotropic lymphoma in a NHP. The invading lymphocytes were CD3 positive and CD20/CD79a negative, confirming a T-cell origin. The etiology of this neoplasm is unclear; however, it may have been secondary to a chronic inflammatory state. No other infections were identified in the small intestine of this animal, although a prominent eosinophilic typhlocolitis with concurrent pinworm infection was noted. Epitheliotropic lymphomas have also been documented in domestic animal species. They are primarily seen in the small intestine of mature cats and, less frequently, in dogs. There is usually a history of chronic inflammatory bowel disease in both species. The cellular infiltrate typically consists of small, darkly stained T cells with irregular nuclear contours invading the epithelium. Small nests of tumor cells may occur, and focal ulceration is a frequent finding. Involvement of the villi is also prevalent, with secondary sloughing and villous fusion. Clinically, animals experience wasting, anorexia, vomiting, and diarrhea associated with chronic malabsorption and inflammation. Human enteropathy-associated T-cell lymphoma (EATL) is a rare non-Hodgkin lymphoma of T-cell origin. The World Health Organization recognizes 2 types of EATL: type I EATL, which constitutes 80%–90% of all cases, and type II EATL, a monomorphic variant of the disease. Type I EATL is associated with celiac disease and the development of a preliminary lymphoplasmacytic inflammation that progresses to atypia and lymphoma. A link between celiac disease and type II EATL has not been demonstrated. Additional characterization of this neoplasm in owl monkeys is warranted to determine its prevalence, as well as any predisposing etiology.

Case 16: Sheila Cummings Macri (Harvard Medical School, New England Primate Research Center)

**History**—A 14-year-old colony-born female cotton top tamarin (*Saguinus oedipus*) with an abdominal mass palpated during routine examination. At necropsy, a 3- to 4-cm-diameter mottled, pink/tan, friable, bilobed mass with multifocal hemorrhage was found to replace the right adrenal gland.

**Morphologic diagnosis:** Adrenal gland: pheochromocytoma and myelolipoma.

**Etiology:** Unknown.
**Discussion:** Pheochromocytomas are neuroendocrine tumors arising from the chromaffin cells of the adrenal medulla. Chromaffin cells are derived from neuroectoderm of the neural crest and produce catecholamine hormones, including epinephrine and norepinephrine. These neoplasms may or may not be functional. Functional pheochromocytomas are known to induce hypertension, pulmonary edema, myocardial infarction, ventricular fibrillation, cerebral hemorrhage, and congestive heart failure in humans. Most cases of pheochromocytomas are well-circumscribed, single, unilateral tumors with larger tumors possessing a definite capsule. The cut surface is typically grey to pink-tan or red with areas of hemorrhage. Large tumors may also have areas of necrosis. The oxidation of catecholamines may darken the tumor to dark red or mahogany after exposure to air. In humans and in bulls, calcitonin-secreting C-cell neoplasms of the thyroid gland occasionally develop concurrently. In a study conducted at the New England Primate Research Center, a number of cotton-top tamarins diagnosed with pheochromocytomas also had concurrent thyroid cystadenomas, implying the possibility of a multiple endocrine neoplasia-like syndrome. Immunohistochemistry is an important tool to diagnosing these neoplasms. Neuroendocrine markers such as chromogranin A, PGP 9.5, NCAM, and SYN are typically positive in pheochromocytomas. Pheochromocytomas are considered uncommon in humans as well as in all domestic and laboratory animals aside from rats and certain mouse strains.

**Case 17: Heather A. Simmons (University of Wisconsin, Wisconsin National Primate Research Center)**

**History**—A 2.9-year-old female cynomolgus macaque (*M. fascicularis*) on a terminal infectious disease study. This animal was euthanized at the planned experimental end point.

**Morphologic diagnosis:** Liver: hepatitis, multifocal, mild with intrasinusoidal erythrophagocytosis and intraerythrocytic merozoites, trophozoites (small ring forms), and rare schizonts consistent with *Plasmodium spp*.

**Etiology:** *Plasmodium inui*.

**Discussion:** *Plasmodium inui* is one of approximately 14 plasmodium species that infect Old World primates. *P. inui* is considered mildly pathogenic and is widespread throughout Southeast Asia. Natural hosts include *M. fascicularis* and *M. nemestrina* and may persist in animals for years. In natural hosts, little to no clinical disease is reported, whereas aberrant hosts may have severe and debilitating disease. The basic plasmodium life cycle consists of 2 phases: the sexual phase within the mosquito and the asexual phase within the vertebrate host. In the vertebrate host, an extracellular phase occurs in host hepatocytes, and the erythrocytic phase occurs within the circulatory system. Clinical signs in macaques may include fever, depression, anorexia, weight loss, anemia, leukopenia, and diarrhea. The onset of fever coincides with rupture of infected erythrocytes. Although malaria is considered ubiquitous in macaques imported from Asia, infection may confound the interpretation of results in a research setting.
Case 18: Audrey Baldessari (University of Washington, Washington National Primate Research Center)

**History**—A captive-bred 4.5-month-old male pig-tailed macaque (*M. nemestrina*) presented with enlarged cranium, ataxia, and nystagmus. Cranial sutures were open.

**Morphologic diagnosis**: Cerebellum and brain stem: malignant embryonal neuroepithelial neoplasm.

**Etiology**: Unknown.

**Discussion**: A diagnosis of ependymoblastoma was favored for this embryonal neuroepithelial neoplasm with the differential diagnoses, including other embryonal neoplasms (medulloblastoma) or ependymoma. The neoplasm caused effacement of the brain stem architecture, compression and invasion of the cerebellum, and secondary hydrocephalus.

Ependymoblastoma is an extremely rare childhood neoplasm and may affect any level of the central nervous system. The rosettes in this type of neoplasm are critical to its diagnosis and are called “ependymoblastic” or ependymal rosettes. These rosettes are expected to stain positively with vimentin and focally positive with glial fibrillary acidic protein. This type of rosette is also seen in anaplastic ependymomas; however, in this case, the young age of the animal as well as cell morphology and sparse intralesional necrosis helps to differentiate ependymoblastoma from an anaplastic ependymoma. Hydrocephalus is most commonly caused by the obstruction of outflow of cerebrospinal fluid from the brain’s ventricular system, which can be caused by tumors (ependymoma/ependymoblastoma, PNET, medulloblastoma), hemorrhages, infections, or congenital malformations. Although hydrocephalus has been documented in macaques, this case represents the first known report of malignant ependymoblastoma with secondary hydrocephalus in an infant pig-tailed macaque.

Case 19: Prachi Sharma (Emory University, Yerkes National Primate Research Center)

**History**—A colony-born 4-year-old pig-tailed macaque (*M. nemestrina*) innoculated with simian human immunodeficiency virus. Chronic diarrhea, weight loss, and tremors in the right arm and both legs were observed at approximately 2 months postvirus.

**Morphologic diagnosis**: Lung: interstitial pneumonia with intranuclear and intracytoplasmic inclusions, multifocal, severe.

**Etiology**: Cytomegalovirus (CMV).

**Discussion**: Cytomegalovirus, a beta group herpesvirus, can be asymptomatic or produce disease depending on the age and immunologic status of the animal. The virus infects and remains latent in white blood cells, from which it can be reactivated when cellular immunity is depressed. Transmission of CMV can be iatrogenic, transplacental, or mucosal through breast milk, saliva, cervical, or vaginal secretions. Cytomegalovirus in immunosuppressed individuals occurs most commonly in patients with AIDS or recipients of solid organ or
bone marrow transplants. Life-treatening disseminated infections may involve pneumonia, colitis, and retinitis. Cytomegalovirus infections of baboons, African green monkeys, and rhesus macaques have been reported.\textsuperscript{62} Rhesus CMV (RhCMV) is commonly enzootic in populations of macaques, with immunocompetent animals remaining asymptomatic after natural or experimental infection.\textsuperscript{37} Rhesus CMV infection results in lifelong asymptomatic persistence in immunocompetent animals and significant morbidity and mortality in immunocompromised macaques.\textsuperscript{5} Macaques experimentally infected with RhCMV\textsuperscript{14} or coinfected with RhCMV and SIV exhibit clinical signs similar to those in CMV-infected humans.\textsuperscript{57}

**Case 20: Cynthia L. Courtney (Emory University, Yerkes National Primate Research Center)**

**History**—A 53-year-old female chimpanzee (\textit{P. troglodytes}) presented with emesis, diarrhea, and lethargy.

**Morphologic diagnosis:** Duodenum: duodenitis, lymphoplasmacytic, diffuse, moderate with villus blunting and crypt abscesses.

Duodenum: adenomatous hyperplasia of Brunner’s glands, marked.

**Etiology:** Unknown.

**Discussion:** Adenomatous hyperplasia of Brunner’s glands has been reported in several species of NHPs, including a rhesus macaque, chimpanzee, and baboon.\textsuperscript{10,17,69} In humans, tumors of the duodenum arising in relation to the glands of Brunner are uncommon, with an estimated incidence of 0.08%.\textsuperscript{71} Most tumors of the Brunner’s glands are single adenomas with diffuse adenomatous hyperplasia reported infrequently.\textsuperscript{71} The normal function of the Brunner’s glands is secretion of alkaline fluid; therefore, these glands appear to protect the duodenal mucosa from the damaging action of acidic chyme.\textsuperscript{20} Brunner’s glands are most numerous in the first portion of the duodenum, beginning just distal to the pylorus and gradually diminishing toward the second and third portions—thus, the anatomical distribution reflects their physiological role. Brunner’s gland hyperplasia or adenoma is a rare benign condition of the duodenum, with fewer than 200 cases reported.\textsuperscript{20} Size is the critical feature in the arbitrary distinction between adenoma and hyperplasia. Adenomas are larger than 1 cm, and hyperplasia refers to multiple lesions usually less than 1 cm.\textsuperscript{20} About 15\% of patients with chronic renal failure have hyperplastic Brunner’s glands detected at endoscopy as multiple polyps in the duodenal bulb.\textsuperscript{48}

**Conclusion**

All the great apes are in peril in their countries of origin in Africa and Asia from a combination of factors, such as habitat loss, human population encroachment and direct predation by humans, and disease. Apes housed in zoos and sanctuaries throughout the world are affected by some of the same health issues as their wild counterparts. Some diseases are either specific to the captive situation or exacerbated by it. Although much is known, more extensive investigation of health and mortality of all the great apes are
desperately needed. Pathology is essential for understanding causes of morbidity and mortality that can be prevented or treated, both in the wild and in zoos. Similarly, New World primates face extreme and unrelenting pressure due to habitat loss. Disease status in wild populations is poorly monitored, and most of the knowledge gained is from captive animal collections. Many disease outbreaks in captive animals can be related to management practices that do not adequately consider exposure to sources of infection, ranging from exposure to infected wild rodents, raccoons, and birds to contaminated food sources. Many nonclinical pharmacology and safety studies use NHPs, in particular macaques. New sources are being utilized to meet increased need, and these varied sources bring forth genetic diversity and different incidences of background findings and pathogens. The accuracy of animal information from some suppliers may be incomplete and shipments may pool NHPs from various farms and/or countries creating the opportunity for disease transmission and outbreaks in susceptible groups. The small numbers of animals used in drug safety studies (often only 3 or 4 animals per group) pose an additional challenge to interpretation of pathology findings in NHPs. Thus, in drug safety assessment, there still is a great need for knowledge and expertise in understanding background findings and pathogens as related to the age, source, strain, and disease status of NHPs. A broader understanding and documentation of lesions can help clarify background from treatment-related findings and go a long way in reducing potential confounding problems for design and interpretation of safety/biomedical studies.

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