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Chapter 15

Apes

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INTRODUCTION

Apes are Old World primates found in Southeast Asia and Africa. The group includes the gibbons or lesser apes (family Hylobatidae), and the great apes (family Hominidae): bonobos (pygmy chimpanzees), (common) chimpanzees, gorillas, and orangutans. Many ape species are found in zoos, including several of the 17 species of gibbons, common chimpanzees, bonobos, western lowland gorillas, and Bornean and Sumatran orangutans. In terms of diseases and pathology, the common chimpanzee is the best studied of the apes, largely due to large laboratory colonies and longstanding field studies (Gamble et al., 2004; Laurence et al., 2017; Schmidt 1975; Terio et al., 2011). Most literature on diseases of other apes concerns zoo-housed animals; however, the literature on free-living western lowland and eastern (mountain) gorillas is expanding (Benirschke and Adams, 1980; Cousins, 1972, 1983; Hewitt, 2005; Janssen, 1993; Janssen and Bush, 1990; Lowenstine et al., 2008, 2016; Meehan and Lowenstine, 1994; Munson and Montali, 1990; Nutter et al., 2005a; Strong et al., 2016).

The IUCN lists all apes as endangered or critically endangered (http://www.iucnredlist.org) (see Table e1 in the Supplemental Materials for the current taxonomic list and conservation status). Threats to wild populations include: hunting for bush-meat trade; exploitation for pet trade; accidental entrapment in snares set for other animals; habitat loss due to deforestation for firewood, commercial logging, mining and palm oil plantations; wildfires created by human activities, and nonanthropogenic factors including climate change and predation by large felids (D'Amour et al., 2006). African apes are also threatened by diseases, such as Ebola virus, anthrax-like infection and respiratory diseases (Walsh et al., 2003; (Leendertz et al., 2006).

UNIQUE FEATURES

Extensive review of ape special anatomy is beyond the scope of this chapter. The reader is referred to physical anthropology/primatology texts (e.g., Ankel-Simons, 2007; Gibo, 2014; Gregory 1950; Swindler and Wood, 1982) and refereed literature (e.g., Gibbs et al., 2002; Lowenstine, 2003; Strauss, 1937). Notable gross and histologic features that impact interpretations by pathologists are noted in the following sections and in the Supplemental Materials that accompany this chapter.

NON-INFECTIOUS DISEASES

Nutritional

A syndrome of **regurgitation and reingestion** is described in zoo-housed gorillas, bonobos, chimpanzees and orangutans (Miller and Tobey, 2012). It can be mitigated by increasing the fiber, the amount of browse in the diet or opportunities to feed (Less et al., 2014). Damage to dental enamel is the only described related pathological correlate.

In apes, **protein deficiency** is occasionally seen in captive or rehabilitation settings. The protein requirement of apes is similar to that of Old World (OW) monkeys (~14% on a dry matter basis in young chimpanzees, less in adults) (NRC, 2003). Protein deficiency in orphaned, young lowland gorillas is associated with chronic alopecia along the back and legs, hair color change from black to gray or brown, poor growth, weight loss, normocytic normochromic anemia, and hypoalbuminemia (Mundy et al., 1998).

Both **Vitamin D deficiency** (rickets, osteopenia, metabolic bone disease) and **Vitamin C deficiency** (scurvy, scorbutic rickets) can occur in apes. Lesions are similar to those in OW monkeys (see Chapter 14).

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Obesity is a common problem in many zoo apes, especially gorillas and orangutans. **Metabolic syndrome** in female chimpanzees is linked to obesity and likely also exists in other apes (Steinetz et al., 1996). Clinical parameters include increased abdominal fat (measured by increased waist/umbilical girth circumference), increased fasting blood glucose and triglycerides, decreased high density lipoproteins, and elevated blood pressure (Ely et al., 2013; Videan et al., 2007). Morbid obesity is associated with hypothyroidism, hypertensive heart disease, and stroke in adult orangutans (Lowenstine et al., 2016).

Iron overload in zoo-housed apes is most common in follivorous and frugivorous species (gorillas, orangutans and gibbons), and is rare in mountain gorillas except in starvation (Lowenstine and Stasiak, 2014). Grossly, there may be orange/brown discoloration of the duodenal mucosa and bronze discoloration of the liver. Histologically, hemosiderin is present in tingible body macrophages in the duodenal villous lamina propria, hepatocytes (periportal to panlobular), and Kupffer cells. Susceptible species have likely evolved enhanced mucosal absorption (no mucosal blockade) to compensate for natural diets high in tannins and other phytochemicals that bind iron in the intestinal lumen. Molecular aspects of ape iron balance have not been investigated. Chronic disease (e.g., mycobacteriosis) or captive diets high in ascorbic acid and low in fiber that enhance iron absorption can lead to iron sequestration and cause or exacerbate iron overload.

Metabolic

Type II diabetes and insulin resistance are associated with obesity in female chimpanzees (Andrade et al., 2011). Type II diabetes, defined by elevated fasting glucose and hemoglobin A1C, occurs in about 1% of all laboratory-housed chimpanzees and 3.7% in chimpanzees over 30 years of age (McTighe et al., 2011). Elevated fasting glucose levels are also noted in about 6.7% of zoo housed orangutans with levels suggestive of prediabetes and diabetes when evaluated in concert with fasting insulin (Gresl et al., 2000). Overweight adults, both male and female, are usually affected. However, weight or age alone does not correlate with fasting insulin and glucose levels. Histological lesions in the islets of Langerhans seen in several other species have not been described in diabetic apes.

Congenital/Genetic

All great apes have a diploid number of 48 chromosomes (humans have 46). The number of chromosomes in gibbons varies from 2N = 38 to 52. **Chromosomal defects** in apes that are lethal in infancy include **trisomy 22** (analogous to human trisomy 21, Down syndrome) in a chimpanzee and a Sumatran orangutan, and **trisomy 18** (analogous to trisomy 19 in humans) in a bonobo. In addition to fetal loss, phenotypic characteristics suggesting karyotypic anomalies include low birthweight, delayed developmental milestones, weakness, poor nursing, dull mentation, prominent epicanthic folds, syndactyly, protrusion of the tongue, abnormal pinnae, flat facial plane, spinal anomalies, and heart defects (Andrle et al., 1979; Lear et al., 2001; McClure et al., 1969). Congenital hypothyroidism can have similar signs. Karyotypic anomalies identified in adults include **triple X** in a female gorilla (similar to XXX Turner's syndrome), and a **3q deletion** (analogous to human deletion 4q) in a male gorilla (Bradford et al., 2013).

Syndactyly (interdigital webbing) is the most common congenital defect in eastern gorillas, occurring in >50% of mountain gorillas (Mudakikwa et al., 2001). Webbing between the second and third toes is normal in the siamang gibbon, hence the species name *syndactylus*.

Linear enamel hypoplasia (LEH) and **localized enamel hypoplasia of the primary canines (LHPC)** are the most common **dental anomalies** in apes in captivity and in the wild (Hannibal and Guatelli-Steinberg, 2005). Defects occur in either deciduous or permanent teeth and may involve one or multiple teeth (Fig. 15.1). The pathogenesis involves transient disruption of enamelogenesis due to internal stressors, such as disease, or environmental stressors, such as climatic events that disrupt food availability (Guatelli-Steinberg et al., 2012). Synthesis of several studies confirms that, in general; orangutans are most affected followed by chimpanzees and gorillas, though in sympatric western lowland gorillas and chimpanzees, the gorillas were more often affected. The influence of fluoridation of city water on enamel dysgenesis in zoo-housed apes has been suspected, but not proven.

Several **cardiac defects** are described in apes including: atrial and ventricular septal defects in orangutans, ventricular septal defects in a premature chimpanzee and a gorilla, and coarctation of the aorta in a gorilla (Greenberg et al., 1999; Trupkiewicz et al., 1995). None are species specific or of population concern.

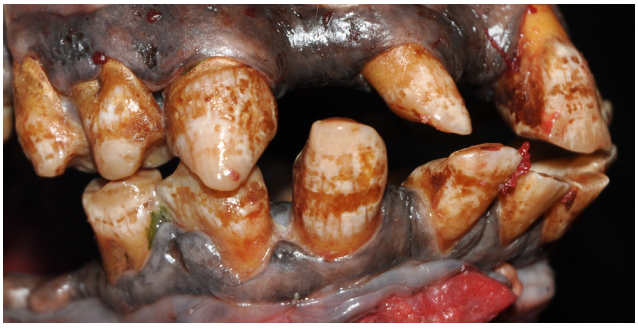

FIGURE 15.1 Linear enamel hypoplasia and pitting of enamel in a geriatric orangutan. Hypoplasia is characterized by horizontal bands of decreased thickness or absent enamel. Tooth loss, gingival regression and periodontal disease are also present.

Age-Related/Degenerative

The most significant degenerative diseases of captive ape populations are **cardiovascular disease, renal disease**, and **arthritis**. Neurodegenerative diseases also occur and are important in apes and for comparison with human dementias. Several of the most important of these diseases are described below. Additional information on the pathology of aging in apes can also be found in a recent review by Lowenstine et al. (2016).

Cardiovascular disease (CVD) is a significant factor in deaths of zoo and laboratory housed apes being reported in 45% of bonobos, 41% of gorillas, 38% of zoo chimpanzees, >50% of colony chimpanzees, and 20% of orangutans (Gamble et al., 2004; Lammey et al., 2008; Laurence et al., 2017; Lowenstine et al., 2008; McManamon and Lowenstine, 2012; Meehan and Lowenstine, 1994; Seiler et al., 2009). Gibbons are affected with unknown prevalence. Cardiovascular disease, often incidental to cause of death, is also recognized in free-living chimpanzees and eastern gorillas (Kambale et al. 2014; Nutter et al., 2005b; Terio et al., 2011).

Normal heart weights (HW) and measurements are not established for the apes. Data from a limited number of zoo-housed gorillas indicate that adult male heart mass ranges from 449 to 1600 g (Benirschke and Adams, 1980) [data compiled by Gorilla Species Survival Plan (SSP) in 2016]. Adult male hearts without overt heart disease range from 449 to 720 g; hearts with mild fibrosis or hypertrophy 720 to 820 g; and hearts from apes with confirmed heart disease range from 725 to 1600 g. The heaviest hearts are dilated as well as hypertrophied. Heart weights of laboratory chimpanzees, from colonies with a high prevalence of sudden cardiac death, range from 195 to 450 g (HW/BW [body weight] 0.39% to 0.94%) for females, and 275 to 660 g (HW/BW 0.46%–1.06%) for males (Lammey et al., 2008). The most frequent cardiac lesion in all four taxa is **dissecting myocardial fibrosis** (Schulman et al., 1995); also seen are **aortic dissection, atherosclerosis,** and **valvular disease**. Because of the importance of CVD in the apes, special cardiac necropsy protocols have been developed (https://greatapeheartproject.org/projects/postmortem). These protocols standardize data collection and should be followed to enable development of consensus terminology in line with best practices for human and veterinary cardiology (Sheppard, 2012).

Sudden or anesthetic deaths, presumably from fatal arrhythmias, are often associated with **dissecting myocardial fibrosis**. This is typically a condition of adult male gorillas and chimpanzees in their mid 20s and older, though it can occur in younger males and in females. Grossly, affected hearts often have pale streaks or patches of tan or grey myocardial discoloration that corresponds histologically to fibrosis or steatosis. Often also noted is increased cardiac mass, frequently due to left ventricular hypertrophy (Fig. 15.2), and less often globoid enlargement with biventricular dilation. Female gorillas, orangutans and some chimpanzees may have extensive fibrosis without left ventricular hypertrophy. Histologically, dissecting fibrosis (Fig. 15.3), often radiating from intrinsic coronary arteries, is seen in the myocardium of all four chambers including the trabeculae carnae and papillary muscles. Large blocks of fibrosis suggestive of myocardial infarction are infrequent. Fibrosis is seen in both hypertrophied and dilated hearts and is usually associated with little or no inflammation. When present, inflammation is centered on individual myofibers. Myofiber hypertrophy with karyomegaly (representing polyploidy) and atrophy of entrapped myofibers can occur in the same heart. The polyploid nuclei in affected hearts are often distorted as well as enlarged.

Fibrosis is a common endpoint in many disease processes, and it is likely that the pathogenesis of myocardial fibrosis in

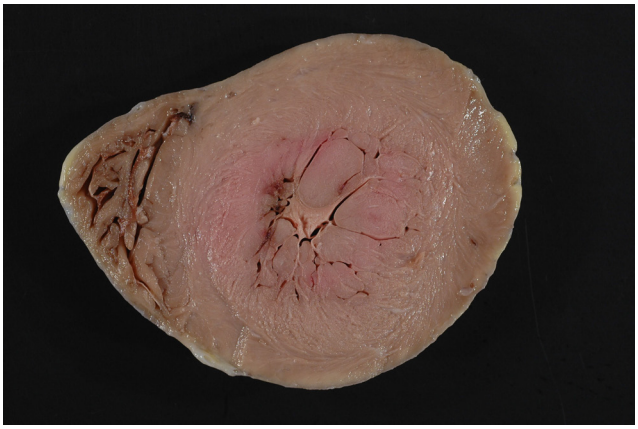

FIGURE 15.2 Cardiomegaly and left ventricular hypertrophy in a common chimpanzee. Transverse short axis section taken 3 cm from the apex of the heart.

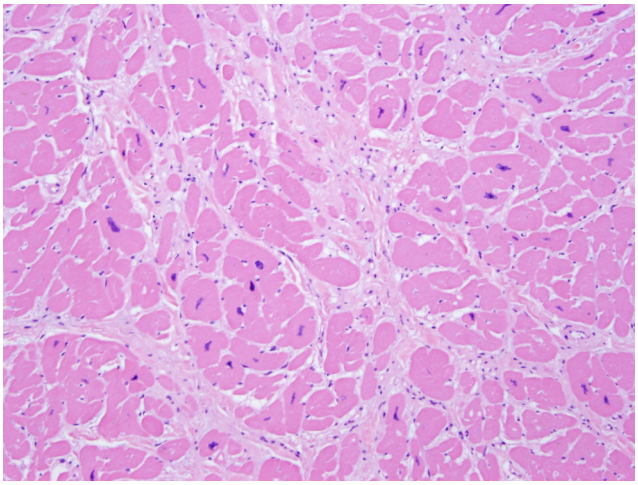

FIGURE 15.3 Myocardial fibrosis in a geriatric common chimpanzee. The interstitium is mildly to moderately expanded by fibrosis. Fibrosis is associated with atrophy of some and hypertrophy (indicated by karyomegaly) of other entrapped myocardiocytes.

apes is heterogeneous. This is reflected in the various names applied to the syndrome (fibrosing cardiomyopathy, idiopathic myocardial fibrosis, interstitial myocardial fibrosis, hypertrophic cardiomyopathy, and dilated cardiomyopathy). The latter two designations may apply to different stages of the same process, as dilated hearts in apes are usually heavy, indicating prior hypertrophy (Sheppard, 2011). Left ventricular hypertrophy and arteriosclerosis of intramural coronary arteries indicate that hypertension may be involved in the pathogenesis of ape myocardial fibrosis (Lowenstine et al., 2016; Miller et al., 1999; Susic and Frohlich, 2008). Factors linked to hypertension in humans may also affect adult apes. These include age-associated increased arterial stiffness, chronic inflammatory conditions, abnormal sympathetic nervous system activity, psychosocial stress, metabolic syndrome, age-associated increased salt sensitivity, and chronic renal disease. Documenting ante mortem indirect blood pressure measurement in apes is challenging. Anesthetics can alter blood pressure, and measurements without anesthesia require special training of keepers and apes and validation of equipment and techniques. Hyaline arteriosclerosis and arteriolosclerosis consisting of medial smooth muscle hypertrophy and hyalinization with thickening or splitting of the internal elastic membrane of intramural (intrinsic) arteries of the heart is the dominant vascular change in gorilla hearts (Fig. 15.4). It is present, but inconsistent, in chimpanzee and orangutan hearts. Systematic examination of vessels in other organs (e.g., eyes and kidney) to corroborate cardiac-related hypertensive changes (Fig. 15.5) are important goals in ape necropsies (Neimuth et al., 2014). Although inflammatory myopathies due to both viruses (e.g., encephalomyocarditis virus, Coxsackie virus) and protozoa (trypanosomes) do occur in apes, the preponderance of ape heart disease is not inflammatory at the time of diagnosis.

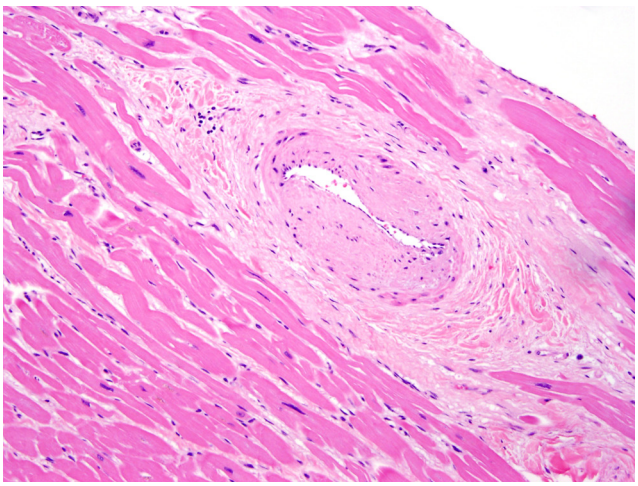

FIGURE 15.4 Arteriosclerosis in an intrinsic coronary arteriole in a common chimpanzee. Changes are characterized by medial smooth muscle hypertrophy and hyalinization.

Thoracic aortic dissection is the second most common cardiovascular lesion in gorillas, is an important problem in bonobos, and is rare in chimpanzees and orangutans (Kenny et al., 1994; Lowenstine et al., 2016, SSP data, unpublished). Dissections generally begin in the ascending aorta (Debakey type II, Stanford type A) just distal to the aortic valves, or within an aortic sinus. Aortic dissection occurs with or without aneurysm. Dissections may result in a "double-barreled aorta" with blood in both the old lumen and within the mural defect (Fig. 15.6). Death is due to pericardial hemorrhage and tamponade, acute adventitial hemorrhage that disrupts conduction pathways, or hemothorax. Histologically, a frequent change is "cystic mucinous medial

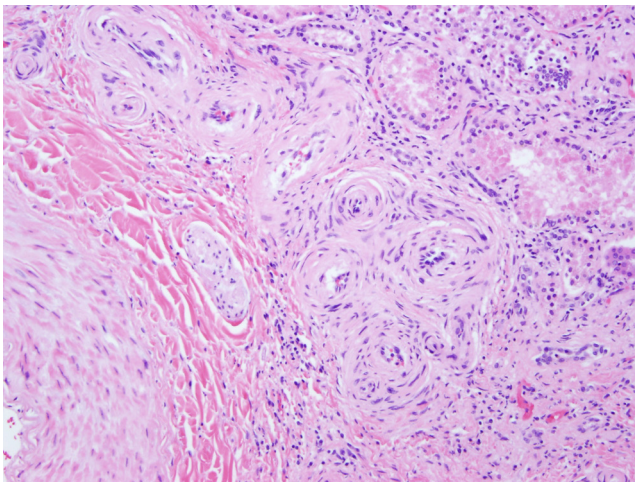

FIGURE 15.5 Renal arteriolosclerosis due to hypertension in a geriatric male chimpanzee with chronic heart disease. Concentric, hypertrophy of the tunica media with luminal narrowing to occlusion is seen in several renal arterioles.

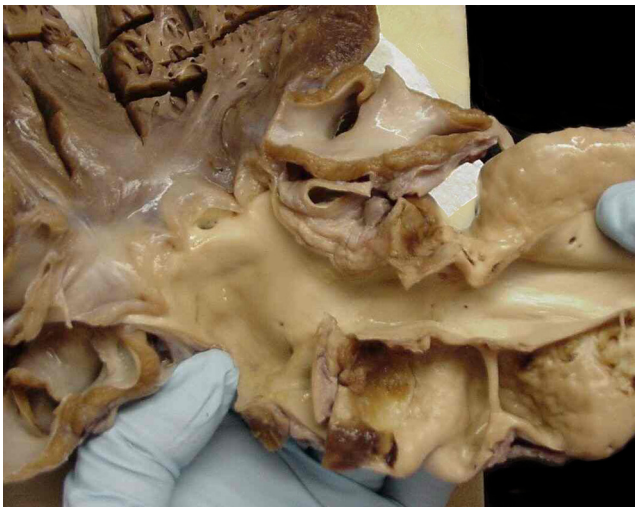

FIGURE 15.6 Aortic dissection in a bonobo. Dissection in the wall of the ascending aorta causes the appearance of a "double barreled" vessel. Note the smooth intima in the true lumen and the roughened lining of the false lumen. *(Photo Courtesy of Disease Investigations, San Diego Zoo Global)*

degeneration" characterized by disorganization or loss of the parallel orientation of elastin fibers, loss of smooth muscle cells, and accumulation of amorphous ground substance (mucopolysaccharides and glycosaminoglycans) between remaining fibers (Fig. 15.7). Inflammation is common in the adventitia, and the vaso vasorum sometimes exhibit arteriolosclerosis (Fig. 15.8). In humans, and likely apes, key risk factors are older age, hypertension, atherosclerosis, pregnancy, and genetic or acquired connective tissue disorders (e.g., Marfan's syndrome, matrix metalloprotease polymorphisms, scurvy, mineral deficiencies) (Goldfinger et al., 2014). These result in an imbalance between dynamic wear and repair mechanisms and inflammation that weakens the aortic wall.

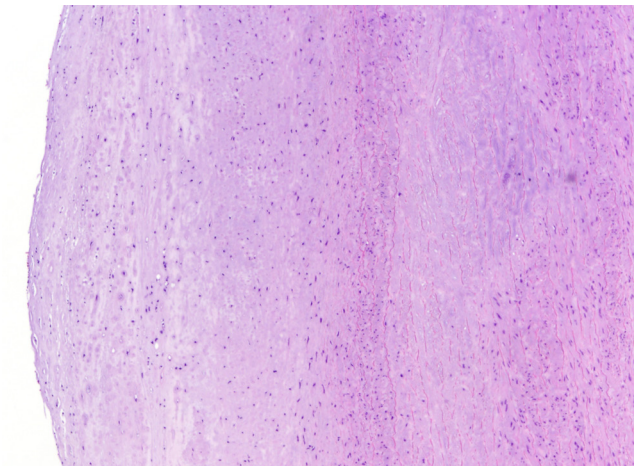

FIGURE 15.7 Mucinous medial degeneration and atherosclerosis in a lowland gorilla. The intima of the aortic arch is markedly expanded by an atherosclerotic intimal plaque to the left of the elastic lamina. Mucinous median degeneration and elastic fiber fragmentation is present on the right.

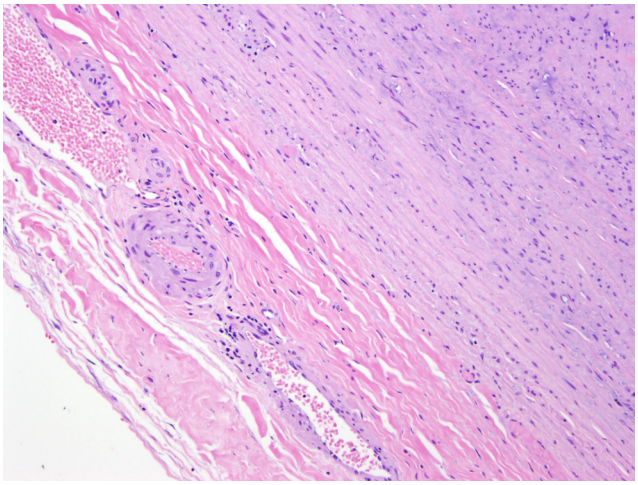

FIGURE 15.8 Arteriolosclerosis in vaso vasorum of the aorta (small vessels on left side of image) in an orangutan. There is moderate mucinous degeneration of the aorta (right side of image).

Coronary atherosclerosis was once common in captive apes, and is now only seen occasionally in very old apes that lived under outmoded husbandry conditions. Atherosclerosis is more common in large elastic vessels, especially the abdominal aorta, iliac arteries, and aortic arch, than in coronary arteries. It can be detected by clinical ultrasound but is more frequently discovered after death (Baitchman et al., 2006). Grossly, atherosclerosis ranges from mild fatty streaks (also occasionally seen in wild mountain gorillas) to complex atheromas with raised ulcerated plaques and "hardening" of the vessel (Fig. 15.9A). Histologically, lipid laden foam cells that accumulate in the intima are accompanied by varying degrees of fibrosis, necrosis and mineralization (Fig. 15.9b). Medial arteriosclerosis with mineralization (Monckeburg's medial calcific arteriosclerosis) is also seen. The pathogenesis of atherosclerosis has been well studied using nonhuman primates as models. It is a complex process, involving alterations in the endothelium, inflammation, dyslipidemia, and changes in the arterial intercellular matrix (Wang et al., 2012). Published lipid values for cholesterol in laboratory chimpanzees and zoo and wild gorillas and orangutans are generally high compared to norms in humans (Steinetz et al., 1996; Schmidt et al., 2005). In chimpanzees, high-density lipoproteins (HDLs) decrease and low-density lipoproteins (LDL) increase with age.

Degenerative and **infective valvular diseases** can occur in captive and wild apes. Echocardiograms in affected gorillas occasionally detect mild mitral regurgitation and mitral valve myxomatous degeneration (endocardiosis) may be seen at necropsy in geriatric free-living mountain gorillas, zoo-housed chimpanzees, and orangutans (Lowenstine et al., 2016; Murphy et al., 2011). In cases of vegetative endocarditis, which most often involves the aortic and mitral valves, both Gram-positive cocci and Gram-negative bacilli have been identified in free-living mountain and captive lowland gorillas (data from Gorilla SSP and Gorilla Doctors).

As occurs in many species, **renal disease** is common in apes as they age. The nature and causes underlying ape renal disease are as yet undetermined. Based on a review of the North American SSP pathology databases, the most common diagnosis in all apes is "chronic interstitial nephritis." Glomerular lesions are frequently reported as well, and proteinuria, suggesting glomerulopathy, occurs in laboratory chimpanzees beginning at about 25 years of age (Videan et al., 2008). Serum urea and creatine increase in males after 25 year and females in their late 30s, but are not associated with clinical renal failure. An interesting aspect of ape renal disease is the statistical correlation with cardiovascular disease. The association in laboratory chimpanzees is known as "cardiorenal syndrome" (Chilton et al., 2016). This syndrome is characterized by glomerular sclerosis and "tubulointerstitial" fibrosis in association with myocardial

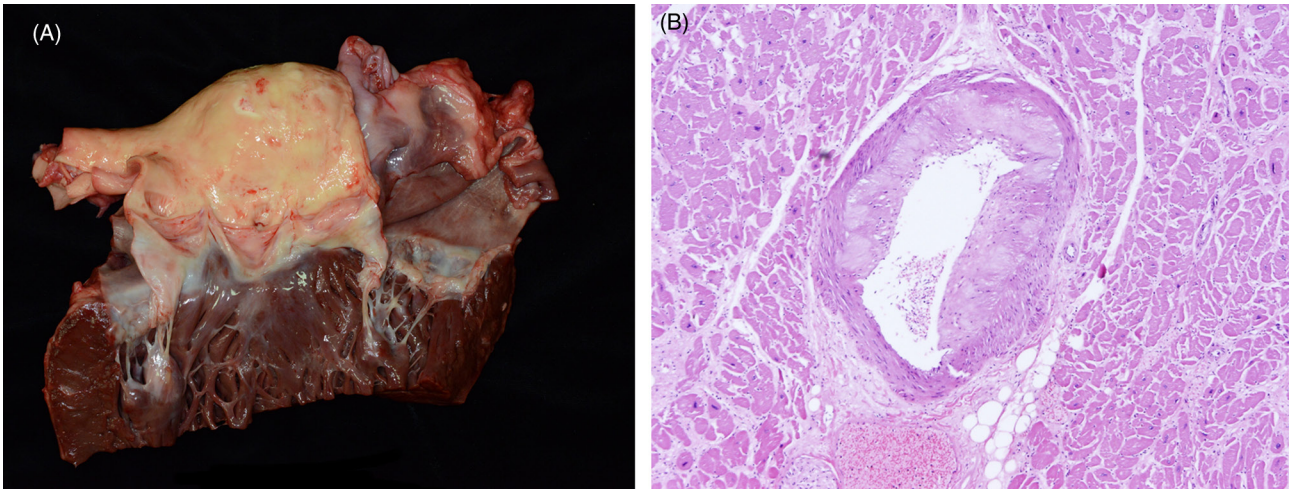

FIGURE 15.9 Atherosclerosis in a lowland gorilla. (A) Multifocal, irregular thickening, and pale yellow discoloration in the aorta is most apparent above the valve leaflet furthest to the right. (B) Characteristic histologic features in an intramural coronary artery include expansion of the intima by eosinophilic material, macrophages, and cholesterol clefts. *(Part A: Photo Courtesy of Disease Investigations, San Diego Zoo Global)*

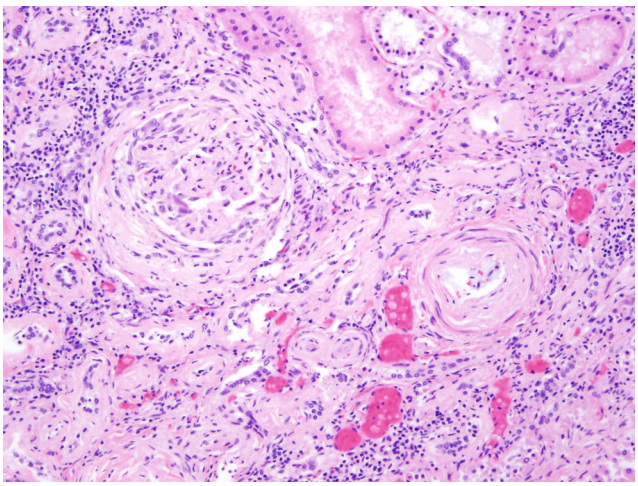

FIGURE 15.10 Cardiorenal syndrome in common chimpanzee. Chronic renal lesions suggestive of hypertension secondary to cardiac disease include glomerular sclerosis and arteriolar concentric medial hypertrophy with luminal narrowing. Also present is chronic interstitial nephritis.

fibrosis (Fig. 15.10). Chronic renal disease can compound heart disease due to increased resistance in the renal vascular bed. Conversely heart disease can lead to renal disease through poor perfusion or from primary hypertension leading to glomerular and renal small vessel sclerosis. Statistically, heart disease and renal disease are also linked in orangutans (Lowenstine et al., 2008).

Both **senile amyloid plaques** and **cerebral amyloid vasculopathy** occur in apes, but *tau* protein deposition (seen in humans) is not common (Lowenstine et al., 2016). Frontal lobes and hippocampus are most affected. Cerebral and meningeal arteriolosclerosis are common, especially in chimpanzees with suspected hypertension (Nunamaker et al., 2012). Strokes have been seen in all species of apes (Borkowski et al., 2000, Jean et al., 2012).

All apes suffer from various forms of **arthritis** as they age, and chronic arthritis with uncontrollable pain is often cause for euthanasia in geriatric apes (Lowenstine et al., 2016). In the wild, post traumatic, monoarticular degenerative joint disease is common. However, both captive and free-living apes, especially chimpanzees and gorillas, appear to suffer from both osteoarthritis and noninfectious, inflammatory, seronegative (nonrheumatoid) polyarticular arthritis with spinal involvement, similar to spondyloarthropathy of humans (Jurmain, 2000; Rothschild, 2005). In addition, mycoplasma-associated, rheumatoid-like arthritis is described in zoo-house gorillas (Munson and Montali, 1990). Factors contributing to development of osteoarthritis in humans that may also contribute in apes include obesity, sedentary lifestyle, genetics, and injury.

Lesions of **osteoarthritis** in apes, similar to those in other species, include cartilage loss on weight-bearing surfaces with sclerosis and eburnation of the exposed subchondral bone in one or more joints, including articular facets of the spine (Fig. 15.11). Rupture of tendons or ligaments is suggestive of post traumatic arthritis. Joint capsule thickening and osteophyte production in response to joint instability can be marked. Cartilage defects in inflammatory arthritis, such as spondyloarthropathy, are more often at joint margins and there may be mineralization and osteophyte production associated with the joint capsule insertion and ligaments and tendons. In the spine, bridging spondylosis involving the margins of the annulus fibrosis can be quite severe, especially in the lumbar area. Independently, degenerative disk disease of the spine can also lead to spondylosis, as can osteoarthritis, which often affects facets as well as

vertebral bodies. Another form of spinal arthritis called **diffuse idiopathic skeletal hyperostosis (DISH)**, a condition in elderly humans, is also thought to occur in apes.

Miscellaneous

Reproductive tract lesions in male chimpanzees include seminiferous tubule degeneration and lymphocytic infiltrates in the prostate gland. **Benign prostatic hyperplasia (BPH)** has been described in chimpanzees at "late middle age" (Steiner et al., 1999). BPH is not reported in the other apes, perhaps because accessory sex glands are not always examined clinically or after death. **Testicular hypoplasia** with hypospermatogenesis and increased interstitial cells is a common finding in Western lowland and mountain gorillas (Fujii-Hanamoto et al., 2011) (Fig. 15.12A, B). Seminiferous tubule atrophy can occur in any ape with chronic illnesses. **Testicular tumors** are rare and include mixed Sertoli-Leydig cell tumor in chimpanzee and interstitial cell adenomas in gorillas (Lowenstine et al., 2016).

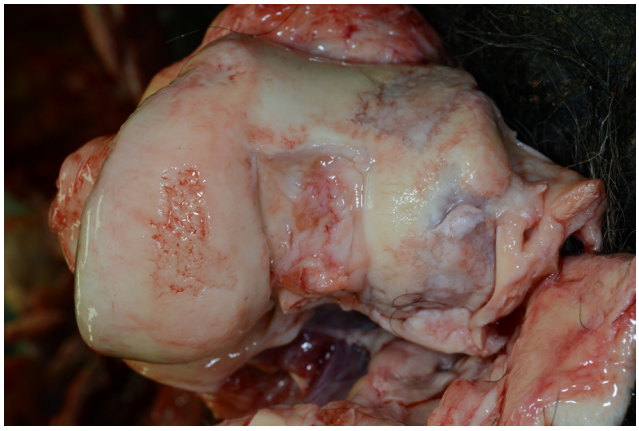

FIGURE 15.11 Osteoarthritis of the femorotibial joint in a Western lowland gorilla. Degenerative changes include severe multifocal loss of cartilage, loss and remodeling of the condyle, and osteophyte formation. *(Photo Courtesy of Disease Investigations, San Diego Zoo Global)*

Ovarian atrophy, uterine leiomyomas, adenomyosis, and **endometrial atrophy** are the most common lesions in the reproductive system of female chimpanzees (Chaffee et al., 2016). Leiomyomas occur in as many as 28% of laboratory chimpanzees, but are infrequent in gorillas, orangutans, bonobos and gibbons (Brown et al., 2009). Although adenomyosis is diagnosed in all apes, including wild mountain gorillas, true endometriosis is very rare but reported in chimpanzee, gorilla, and orangutan. (Doré and Lagacé, 1985; Graham et al., 2009; Munson and Montali, 1990; Nunamaker et al., 2012). **Malignancies of the female reproductive tract** are unusually frequent in zoo-housed gorillas (Lowenstine et al., 2016). They include cervical, uterine, and ovarian adenocarcinomas and a uterine leiomyosarcoma.

The most common **complications of pregnancy** in apes include preeclampsia/eclampsia, retained placenta, placenta previa (placental disk adjacent to or covering the internal cervical os), placenta abruption (premature separation of the placenta), and ascending uterine infections (unpublished SSP data, Halbwax et al., 2009). All apes have hemochorial placentation with deep endometrial invasion and development of maternal decidua (see Supplemental Table e2 for details of ape reproduction). Placental abruption and previa can result in marked vaginal bleeding, dystocia, and death. Ascending infection in gorillas may occur because gorillas allow copulation during the last part of gestation. This can result in weak or dead infants with "infected amnion syndrome" or "in utero pneumonia" characterized by intraalveolar squames with bacteria and associated neutrophils (Fig. 15.13).

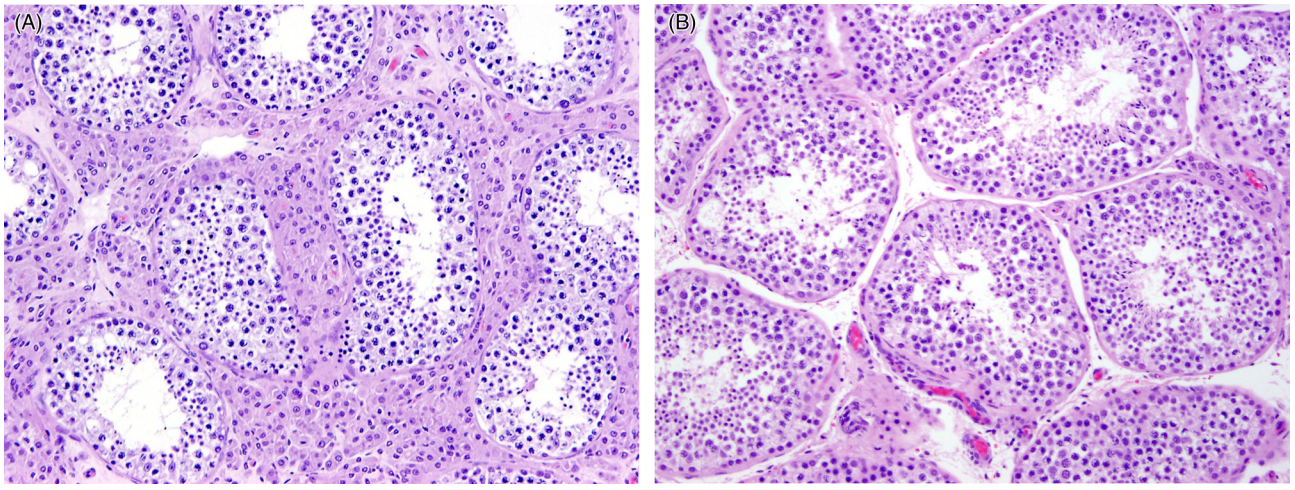

FIGURE 15.12 Normal testes in a western lowland gorilla (A) and chimpanzee (B). (A) Testicular hypoplasia with abundant interstitial cells and hypospermiogenesis is common in gorillas in the wild and captivity and is thought to be within normal limits. (B) Chimpanzees have larger seminiferous tubules and little interstitial tissue in comparison to the gorilla.

Twinning is fairly common in chimpanzees and but infrequent in other apes (Ely et al., 2006). It often results in death of one or both of the infants due to prematurity, low birth weight, or inadequate maternal care.

Infant mortalilty limits population growth in both captive settings and in the wild. Trauma, including infanticide, is an important cause in wild gorillas; infectious diseases and maternal issues also contribute (Hassell et al., 2017). **Prematurity** is a presumed cause of many perinatal deaths in all the apes (Wildman et al., 2011). Gross evidence of prematurity includes low birth weight and open fontanelles. Histological evidence of prematurity, based on data from human neonates, includes: abundant liver extramedullary hematopoiesis (EMH) (Fig. 15.14A) and hepatocellular glycogen; glomerulopoiesis (nephropoiesis is present up to 2 years) (Fig. 15.14B); low degree of pulmonary alveolization; presence of intraalveolar fluid; and the adrenal fetal zone. Evidence of in utero distress or hypoxia in a stillbirth includes meconium staining of the pelage, keratinization and mineralization of thymic epithelium, abundant intralveolar squames and/or meconium, neuronal ischemic necrosis, and in utero involution of the fetal adrenal cortex.

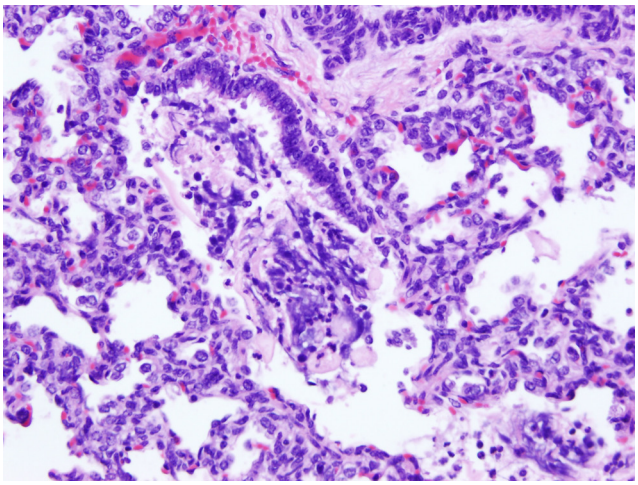

FIGURE 15.13 In utero pneumonia (infected amnion syndrome) in a premature stillborn western lowland gorilla. The condition is characterized by intraalveolar squames and neutrophils in bronchioles and alveolar spaces.

Neoplastic

Neoplasms, including carcinomas, do not seem to be as common in apes as in humans and some other primates (Lowenstine et al., 2016; Varki and Varki 2015). A notable exception is the prevalence of female reproductive malignancies in lowland gorillas, which are rarely seen in other apes. Mammary adenocarcinoma has been reported in a male orangutan (Carpenter and Crook, 2017). Occasional hemolymphatic malignancies are seen in orangutans and gorillas, but leukemia and lymphoma, once common in gibbon colonies, now appear to be rare (Brown and Tarlington, 2017).

INFECTIOUS DISEASES

Apes are host to several unique viruses and are also susceptible to viruses of humans and Old World monkeys. Apes in captivity are in close contact to humans; some groups of apes in the wild are in close contact with humans due to habituation for research and tourism and encroachment of human populations into ape habitats. Serologic surveys show that both captive and free-living gorillas, chimpanzees and orangutans carry antibodies against herpesviruses,

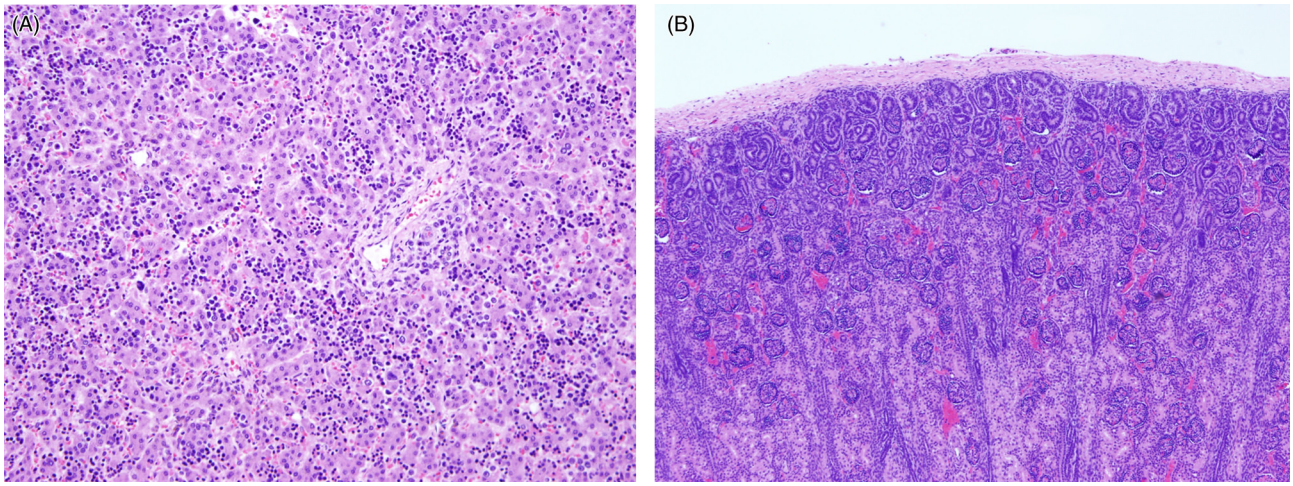

FIGURE 15.14 Histologic features of prematurity in a western lowland gorilla. (A) Findings include abundant hepatic extramedullary hematopoiesis in the liver and (B) renal glomerulopoiesis characterized by fetal glomeruli (small, hypercellular glomerular tufts and prominent peripheral nuclei) and immature tubules (may be dilated, branching, (nephropoiesis), which are coiled and lined by small, cuboidal epithelial cells with closely spaced nuclei).

adenoviruses, paramyxoviruses, pneumoviruses, orthomyxoviruses, and enteroviruses, (Buitendijk et al., 2014; Kalter et al., 1997; Whittier, 2010). Molecular techniques allow for virus detection in noninvasively collected samples, such as feces, urine, and saliva (Köndgen et al., 2010; Smiley Evans et al., 2016). This has revolutionized our ability to screen wild populations for "novel" viruses and to explore viral biome diversity and cross species transfer of pathogens. In addition to notable viral infections in apes discussed later, see the Supplemental Materials Table e3 for an extended list of viruses that have been detected in apes.

DNA Viruses

Poxviruses

Monkeypox virus infection (genus *Orthopoxvirus)* is an OIE listed reportable, zoonotic disease that is endemic to rainforests of central and western Africa where African rope squirrels and other rodents are likely reservoir hosts (Essbauer et al., 2010). Natural infection has been reported in chimpanzees in Africa and in captive chimpanzees, orangutans, gorillas, and a gibbon in Europe (Parker and Buller, 2013; Peeters and Delaporte, 2012). Though monkeypox has not yet been described in bonobos, their range includes endemic areas (Inogwabini and Leader-Williams, 2012). The virus is transmitted by direct contact, ingestion, inhalation, or, possibly via arthropod vectors. Three forms of monkey poxvirus infection occur in nonhuman and human primates: (1) benign upper respiratory signs followed by cutaneous eruptions; (2) mucous membrane lesions, facial and laryngeal edema, and death due to asphyxia; and (3) bronchopneumonia. Incubation in apes is less than 10 days. Initial signs are variable but can include acute death without cutaneous eruptions; cutaneous eruptions without systemic illness; purulent nasal discharge; vesicles on the soles of the feet, back of hands, face and oral mucous membranes; and, in chimpanzees in Africa, nodular lesions on the face. (http://www.oie.int/wahis_2/public/wahid.php/Reviewreport/Review?reportid=20824). The disease can be fatal in orangutans, chimps, and gibbons with as few as 4 days from onset to death.

Eruptions begin as papules and progress to vesicles and pustules that ulcerate and become covered with black scabs. These typical "pocks" are found to have raised margins and depressed centers. Secondary bacterial infections occur; opportunistic *Staphylococcus aureus* infection is common in vesicles and systemically. Lesions typically start on the face, lips and oral cavity and spread over the whole body including the soles of feet. Lymphoid tissues become infected and monocyte-associated viremia leads to systemic disease. Histologically, epithelial proliferation and intra- and intercellular edema with small, inconspicuous eosinophilic intracytoplasmic inclusion bodies involve the epidermis and hair follicles. In humans, intranuclear pseudoinclusions and multinucleated keratinocytes are reported. Internal lesions can include fibrinonecrotic bronchopneumonia and proliferative lesions in the oral cavity and gastrointestinal tract, the latter associated with diarrhea. Batteries of reagents are available to differentiate various poxvirus infections (https://www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10515).

Molluscum contagiosum (MC) is a human disease caused by a poxvirus of the genus *Molluscipoxvirus.* Molluscipoxvirus-like infection is reported in laboratory chimpanzees (Douglas et al., 1967). The prevalence is unknown and it is uncertain if MC in chimpanzees is due to a human or chimpanzee-specific virus. Transmission in humans is by direct contact with skin lesions and fomites or through sexual contact. The route of transmission in chimpanzees is unknown, but reported cases are all juveniles. Lesions consist of small papules with depressed centers on the face, eyelids and inguinal area that regress spontaneously in several weeks. Sebum-like material, expressed from the lesions and examined cytologically with Wright's stain, contains large, basophilic, cytoplasmic inclusion bodies. Histological lesions consist of marked focal acanthosis and hypergranulosis with both elevation and in folding of the epidermis creating a "cup-shaped" lesion. Huge amphophilic, finely granular cytoplasmic inclusions (molluscum bodies) expand the cytoplasm of cells and are pathognomonic (Ishikawa et al., 2015).

Alphaherpesviruses

Human herpesvirus-1 and **2 (HHV-1** and **2; Herpes simplex types 1** and **2)**, are alphaherpesviruses that can cause disease in apes. Serological reactivity to HHV-1 and -2 is common in captive western lowland gorillas, chimpanzees, orangutans, and gibbons (Eberle and Hilliard, 1989; Sakulwira et al., 2002). Molecular evidence of similar viruses is found in wild chimpanzees and western gorillas (Seimon et al., 2015).

Nonfatal **HHV-1 infection** in juvenile eastern gorillas consists of malaise, anorexia and gingival and labial vesicles with ulceration (Gilardi et al., 2014) (Fig. 15.15A). Biopsy reveals epithelial necrosis and vesicle formation with syncytial giant cells containing clear to smudgy intranuclear inclusions (Fig. 15.15B). The oral lesions are identical to those of B-virus infection in macaques. Fatal disease in infant apes is characterized by labored breathing and/or vomiting and diarrhea with rapid progression to death (Heldstab et al., 1981; Kik et al., 2005). Disseminated cutaneous eruptions and vesicles involve the face, chest, and limbs, and there may be ulceration throughout the gastrointestinal tract mucosa. Gross lesions include interstitial pneumonia with or without pericardial effusion, and hepatosplenomegaly. Histologically, multifocal necrosis in lungs, liver spleen, lymph nodes, heart, and brain are associated

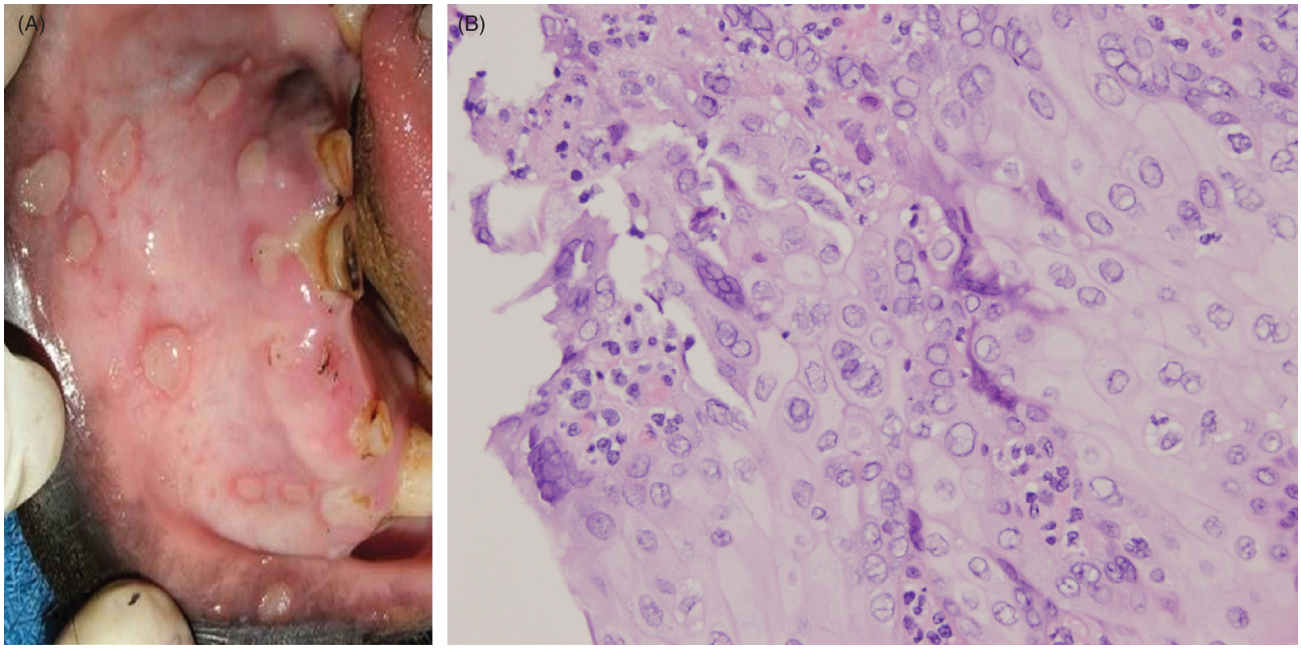

FIGURE 15.15 Human Herpesvirus-1 in an eastern lowland gorilla. (A) Multiple, papular, vesicular, and ulcerative lesions are present in the buccal mucosa. (B) Syncytia with intranuclear viral inclusion bodies characteristic of HHV-1 infection are present in the hyperplastic epithelium at the margin of an oral vesicle. (*Photos Courtesy of Gorilla Doctors*)

with Cowdry type A inclusion bodies. Syncytia with inclusions are most common in the skin, upper gastrointestinal (GI) tract and lung. Cases may be isolated or may occur in the face of illness in adult members of the group.

Fatal infections in gibbons occur as both individual cases and outbreaks (Landolfi et al., 2005). Oral ulcers and vesicles may occur in otherwise healthy animals. Other animals die of encephalitis with or without prodromal oral lesions. Additional clinical signs include lethargy, loss of normal aggression, cranial nerve deficits, paresis and paralysis ending in coma or seizures necessitating euthanasia. Cerebral edema and congestion may be appreciated grossly. Encephalitis is characterized histologically by foci of necrosis, nonsuppurative inflammation, cuffing and multifocal gliosis. Cowdry type A intranuclear inclusions are observed in glial cells and neurons in some, but not all, cases.

Naturally occurring **HHV-2-like virus-infection** causes genital ulcers in colony-housed bonobos and chimpanzees (McClure et al., 1980).

Although as many as 42% of chimpanzees in a colony may have antibodies cross-reactive with HHV-1, HHV-2, or baboon herpesvirus (HVP-2; a gammaherpesvirus), the only verified ape-specific alphaherpesvirus to date is **chimpanzee alphaherpesvirus,** which is related to HHV-2. The primary lesion is oroesophageal ulceration characterized by a red rim with a "whitish" center and resolution in 2–3 weeks (Luebcke et al., 2006). Histopathology is not described; however, the cytopathic effect (CPE) in Vero cells includes necrosis without syncytia.

Varicellovirus (Varicella-zoster; HHV-3; VZV; chicken pox; shingles), also a human alphaherpesvirus, can infect apes (Gray, 2008). Serosurveys demonstrate exposure in chimpanzees, gorillas, orangutans, and gibbons (Kalter et al., 1997). Infection may be lifelong with latency in sensory ganglia and reactivation due to intercurrent diseases or stress. Natural primary infections, similar to chicken pox of children, occur in infant or juvenile captive chimpanzees and gorillas, and experimental work confirms susceptibility of chimpanzees (Cohen et al., 1996; Heuschele 1960; Myers et al., 1987; White et al., 1972). Cutaneous eruptions occur all over the body, especially the trunk, and are characterized by small vesicles that ulcerate and become covered by scabs (Fig. 15.16). Lesions heal without scarring unless pruritis-associated excoriation occurs. Histology in apes is similar to that in humans and OW monkeys, namely epidermal vesicles containing variably sized acantholytic cells with intranuclear inclusions. Systemic signs of disease, such as pneumonia, are not reported in apes. Recrudescent infection in an adult female gorilla consisted of typical cutaneous lesions in a single dermatome and detectable virus in ganglia of that dermatome (Masters et al., 2010).

Betaherpesviruses

Cytomegalovirus (CMV) and ***Roseolovirus*** are members of the *Betaherpesvirinae* subfamily. Cytomegalovirus infections are usually clinically silent, but can cause serious disease in fetuses, infants and immune compromised hosts. Infection is lifelong. Recrudescence occurs due to stressors, such as other viral infections and immunosuppressive drugs. Antibodies reactive with chimpanzee CMV are present with high prevalence in captive western lowland gorillas, chimpanzees, orangutans, and gibbons, and in wild eastern gorillas

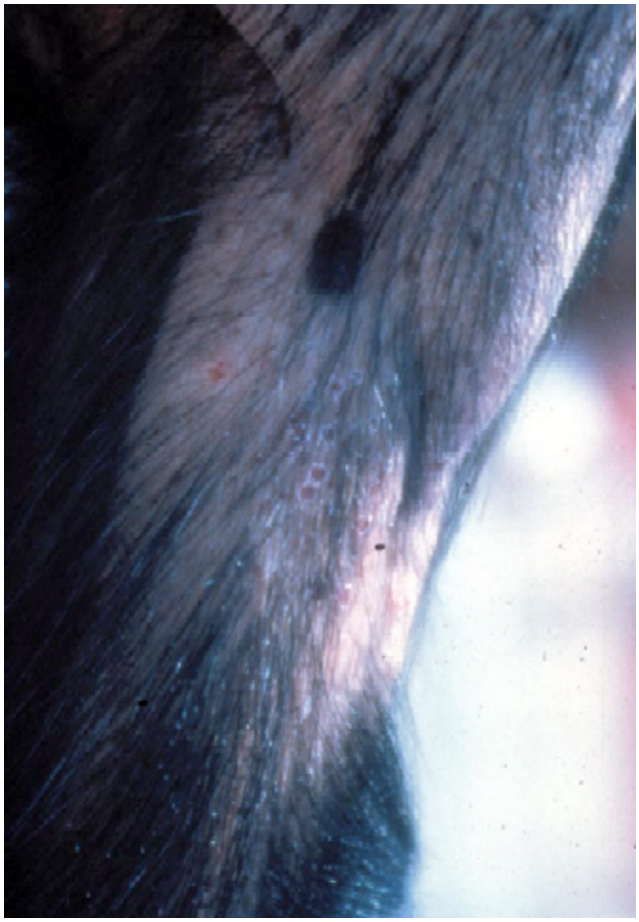

FIGURE 15.16 "Chicken pox" (Varicella zoster) infection in the skin of a chimpanzee. Infection is characterized by multiple, small, round, shallow ulcers resulting from rupture of vesicles. *(Photo Courtesy of L. Gage)*

(Kalter et al., 1997; Sakulwira et al., 2002; Whittier, 2010). In addition, CMVs have been detected by molecular methods in wild western chimpanzees, wild and zoo-housed western lowland gorillas and zoo-housed orangutans with evidence of cross species transmission between gorillas and chimpanzees (Leendertz et al., 2009; Seimon et al., 2015). Clinical disease and deaths are infrequent. Clinical signs of CMV infection are nonspecific including anorexia, abdominal pain or respiratory signs. Histologically, infection is characterized by the presence of "cytomegalic cells" with karyomegaly, amphophilic, Cowdry type A intranuclear inclusions, and ill-defined granular acidophilic intracytoplasmic inclusions, similar to lesions in other primates. Cytomegalic cells are seen in alveolar septa with interstitial pneumonia and throughout the GI tract (including salivary glands), liver, lymphoid organs, brain, eye, and adrenal glands. Lesions are frequently necrotizing and CMV is one of the few viruses associated with neutrophilic inflammation. However, in acute disseminated infection in chimpanzees, cytomegalic cells may be present without inflammation. Associated conditions include adenovirus hepatitis and ulcerative colitis (Davis et al., 1992; Tsuchiya et al., 1970).

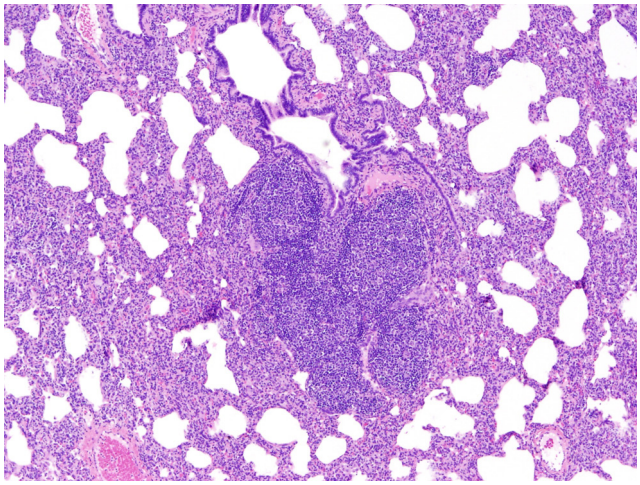

FIGURE 15.17 Gorilla lymphocryptovirus infection in a mountain gorilla. Pulmonary lymphoid proliferation (follicular bronchiolitis and lymphocytic interstitial pneumonia) is thought to be due to a primary lymphocyrptovirus infection.

Gammaherpesviruses

Gamma-1 lymphocryptoviruses (EBV-like viruses) (subfamily *Gammaherpesvirinae*) are found only in primates and are cell associated, lymphotropic, and/or epitheliotropic; they are also potentially oncogenic. The type virus is human Epstein-Barr virus (EBV, HHV-5). Serosurveys show that all apes, including wild mountain gorillas and wild and semicaptive orangutans, have a very high prevalence of antibodies cross reactive with EBV (Kalter et al., 1997; Kilbourn et al., 2003). EBV-like ape viruses are detectable by amplification from peripheral blood mononuclear cells, feces, or saliva in all apes, including gibbons (Ehlers et al., 2010). Cross or shared infection with the same lymphocryptovirus can occur in orangutan and chimpanzee, but there is no known zoonotic potential.

The pathogenicity of chimpanzee, bonobo, gibbon, and orangutan EBV-like lymphocrytoviruses is not well established. Histological lesions suspected to be associated with mountain gorilla lymphocryptovirus include oroesophageal leukoplakia in adult gorillas and follicular hyperplasia in tonsils and lymph nodes, and pulmonary lymphoid hyperplasia (lymphofollicular bronchitis and lymphocytic interstitial pneumonia) in infants (Smiley Evans et al., 2017) (Fig. 15.17). Leukoplakia is characterized histologically by acanthosis, intracytoplasmic edema (ballooning) in cells of the upper stratum spinosum and intranuclear inclusions. These lesions are similar to those reported in immunosuppressed OW monkeys with lymphocryptovirus infection (Carville and Mansfield, 2008). To date there is no proven association between LCV and lymphomas in apes.

Papillomaviruses

Papillomaviruses (family *Papillomaviridae*) are strongly tropic for epithelial surfaces and become latent in basal

epithelial cells. They cause epithelial hyperplasia with characteristic intracytoplasmic edema (ballooning degeneration, koilicytes). Complete virions are formed in the outer stratum spinosum and stratum corneum and result in smudgy amphophilic intranuclear inclusion bodies. **Oral epithelial hyperplasia**, also known as **oral papillomatosis**, is seen in both chimpanzees and bonobos (Hollander and van Nord, 1972; Sundberg et al., 1992; Van Ranst et al., 1991). Clinical disease, generally self-limiting, or lesions seen on routine health exams may be associated with stressful events. Horizontal transmission occurs, possibly through wounding during social interactions. Grossly, lesions on the gums and oral mucosa of the tongue, lips and cheeks are single or multiple, pale pink, plaques or nodules with cobble-stone to villiform surfaces (Fig. 15.18). Histologically they are characterized by acanthosis with irregular branching rete pegs (Fig. 15.19A). There is little cytoplasmic pallor or intracellular edema and inclusion bodies are often inapparent. Immunohistochemistry using antibodies directed towards a papillomavirus group antigen highlights the virions (Fig. 15.19B).

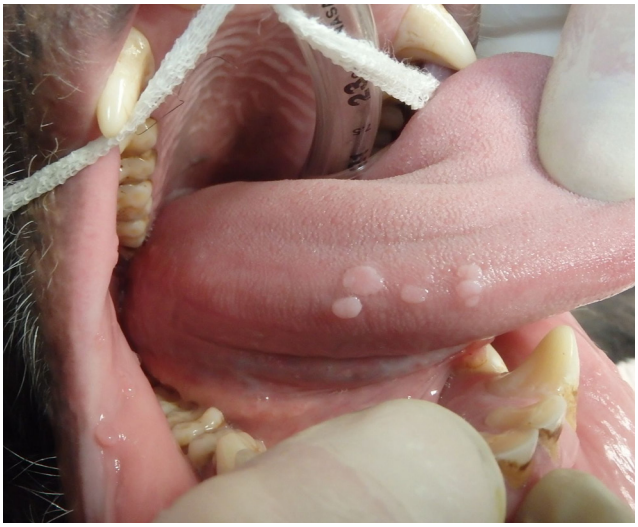

FIGURE 15.18 Chimpanzee papillomavirus infection in the oral cavity of a chimpanzee. Multifocal, demarcated, slightly raised foci of epithelial hyperplasia (papillomatosis) are present on the tongue and buccal mucosa. *(Photo Courtesy of R. Wack, University of California, Davis, Zoological Medicine Service)*

RNA Viruses

Respiratory Disease Viruses

Respiratory infections are a common cause of morbidity and mortality in both captive and wild apes and are second only to trauma as a common cause of death in some wild populations (Buitendijk et al., 2014; Dick and Dick, 1968, 1974; Grützmacher et al., 2016; Kaur et al., 2008; Köndgen et al., 2010, 2011; Lonsdorf et al., 2006; Nutter et al., 2005a; Palacios et al., 2011; Slater et al., 2014; Spelman et al., 2013). These range from self-limiting upper respiratory "colds" to severe lower airway disease and pneumonia that are often complicated by superimposed bacterial infections. Human respiratory disease viruses are infectious for apes as evidenced by natural outbreaks and experimental infection. These include: **rhinoviruses** (*Picornaviridae,* genus *Enterovirus*); **human metapneumovirus** (*Pneumoviridae,* genus *Metapneumovirus)*; **respiratory syncytial virus** (*Pneumoviridae,* genus *Orthopneumovirus*); **measles virus** (*Paramyxoviridae,* genus *Morbillivirus*); **parainfluenza viruses** (*Paramyxoviridae* genera *Respirovirus* and *Rubulavirus*); and **influenza viruses** (*Orthomyxoviridae*, genera *Influenzavirus A, Influenzavirus B, Influenzavirus C*). Respiratory DNA viruses (e.g., adenoviruses, bocaviruses), are also suspected to have reverse zoonotic potential. Definitive diagnosis of

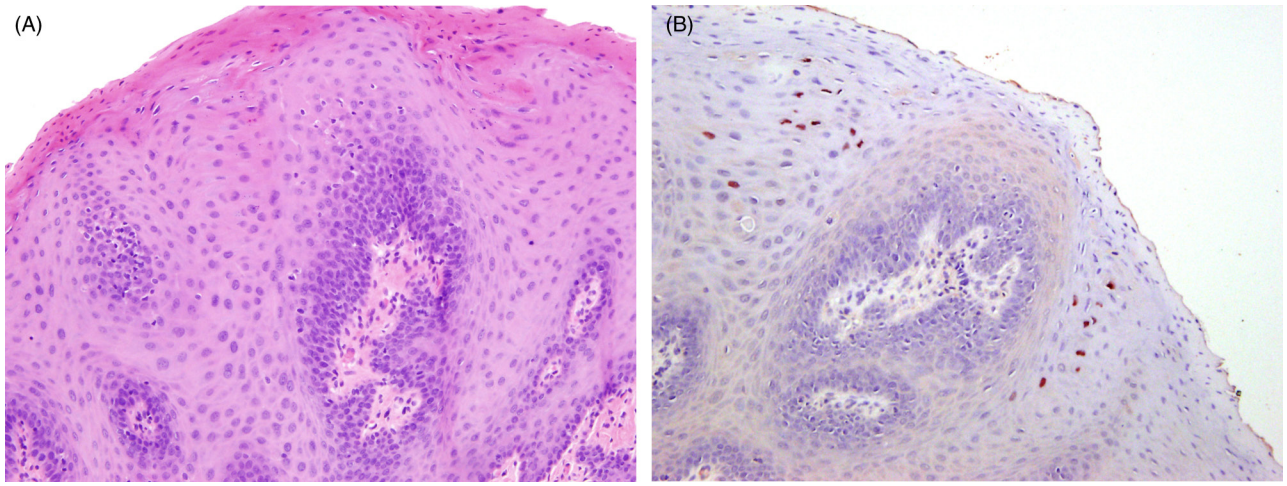

FIGURE 15.19 Oral epithelial hyperplasia in a common chimpanzee. (A) Histologic lesions are characterized by acanthosis with mild hyperplasia of the basal epithelial cell layer. Several smudgy or clear nuclei are seen, but karyomegaly or unequivocal intranuclear inclusions are not. (B) Papillomavirus antigen is demonstrated by immunohistochemistry using antibodies directed toward papillomaviral group specific antigens.

respiratory viral infections relies on histology and virus detection by immunohistochemistry and/or molecular techniques. There are commercially available antibodies for immunohistochemistry for RSV, human metapneumovirus, human parainfluenza viruses 1–3, measles, mumps and others, as well as published sequences for primers for molecular amplification.

First described in humans in 2001, **human metapneumovirus (HuMPV)** (genus *Metapneumovirus*) is a leading cause of upper respiratory disease, bronchitis and pneumonia in children and adults worldwide and is a reverse zoonosis. Naturally occurring, sometimes fatal infections, are recognized in chimpanzees in the wild, in zoos and in free-living, human-habituated mountain gorillas (Kaur et al., 2008; Palacios et al., 2011). Serologic testing suggests widespread exposure to HuMPV in captive apes (Buitendijk et al., 2014). This virus predisposes to *Streptococcus pneumoniae* and other bacterial pneumonias, but viral infection alone can be fatal. Clinical signs include cough and nasal discharge. Grossly, lungs may be firm, mottled and fail to collapse when the chest is opened (Fig. 15.20). Histologic lesions include bronchointerstitial pneumonia with loss of cilia and epithelial necrosis, alveolar epithelial necrosis and fibrin exudation, type II pneumocyte hyperplasia, and airway and alveolar histiocytes (Fig. 15.21A, B). "Smudge cells" may be seen however there are no true syncytia and no inclusion bodies. Although death due to HuMPV occurs in naturally infected apes, experimentally naïve chimpanzees experience only self-limiting nasal discharge.

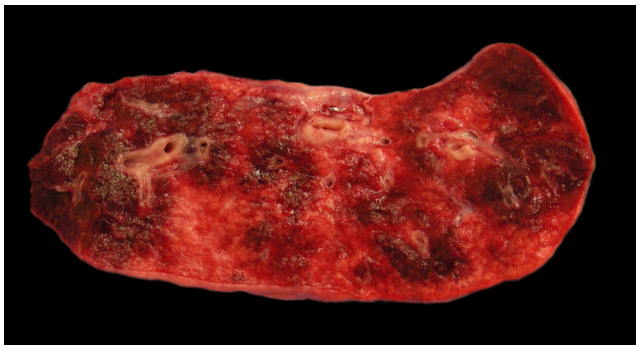

FIGURE 15.20 Human metapneumovirus (HuMPV) infection in the lung of a common chimpanzee. Infection is characterized by nonspecific patchy discoloration and consolidation. *(Photo Courtesy of University of Illinois Zoological Pathology Program)*

Respiratory Syncytial Virus (RSV; genus *Orthopneumovirus*, family *Pneumoviridae*, "chimpanzee coryza agent") was first identified in laboratory-housed chimpanzees and is a reverse zoonosis with humans as natural hosts (Branche and Falsey, 2015). RSV causes upper respiratory disease in humans, providing ample opportunity for transmission to apes in captivity and the wild. Serology reveals antibodies in mountain gorillas and the highest seroprevalence of any of the common human respiratory viruses in zoo-housed great apes (Buitendijk et al., 2014; Whittier, 2010). RSV respiratory disease outbreaks are documented in zoo-housed chimpanzees, gorillas and orangutans (Szentiks et al., 2009; Unwin et al., 2013). In an outbreak in free-living, western lowland gorillas, the strain of RSV was similar to that causing human community acquired respiratory disease (Grützmacher et al., 2016).

Chimpanzees present with sneezing, rhinorrhea, catarrh, and cough (tussis) that often progresses to bronchitis and pneumonia. Severity is highly variable and fatal infections are reported, usually in association with concurrent streptococcal pneumonia. The most severely affected animals exhibit lethargy, anorexia, and weakness. Reddening of the nasopharyngeal mucosa, enlarged tonsils and regional cervical and

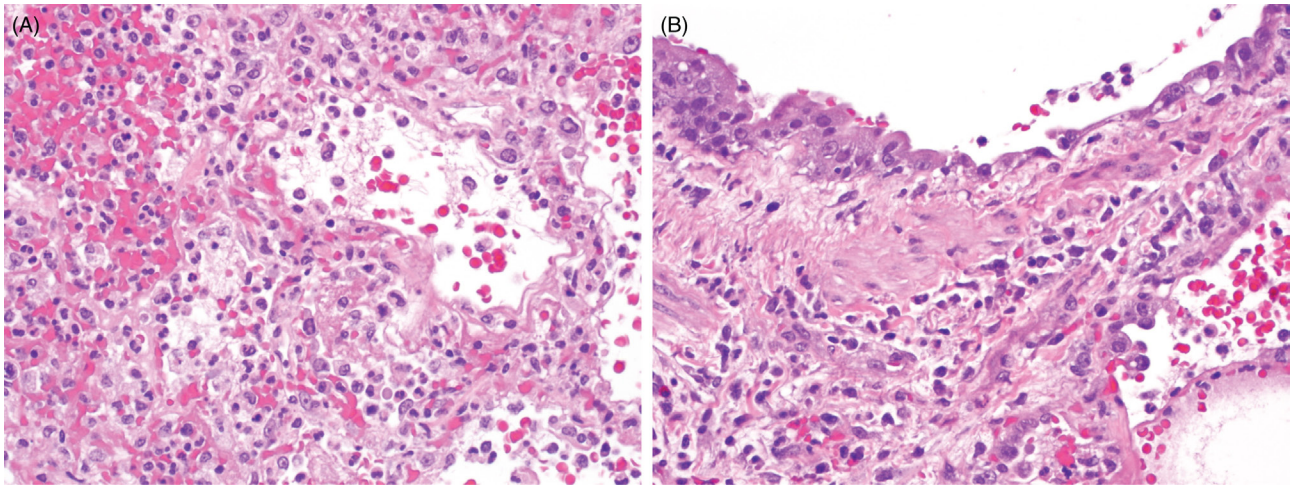

FIGURE 15.21 HuMPV infection in the lung of a common chimpanzee. Bronchointersitial pneumonia is typical of many respiratory viral pneumonias, including HuMPV. (A) Associated lesions include acute alveolar septal damage and fibrin exudation. Neutrophils may be responding to secondary bacterial infection. (B) Bronchiolar damage includes characteristic epithelial deciliation *(on left)* and attenuation *(on right)*. *(Photos Courtesy of University of Illinois Zoological Pathology Program)*

tracheobronchial lymph nodes, pulmonary edema and patchy to panlobar pulmonary consolidation with fibrinous pleural adhesions are features in fatal cases. Histologically there is a typical viral bronchointerstitial pattern with small airway epithelial necrosis or proliferation and occasional multinucleated syncytia with intracytoplasmic acidophilic inclusion bodies. Suppurative bronchopneumonia is present if there is secondary bacterial infection, in which case viral "foot prints" may be largely effaced. Diagnosis is based on histology and detection of the virus by PCR or IHC. Measles bronchointerstitial pneumonia is a main differential diagnosis, but in measles both intranuclear and intracytoplasmic inclusions are present and the GI tract is often affected.

Measles (rubeola) virus (genus *Morbillivirus*) is a highly contagious infection of humans that occurs as periodic epidemics in children and unvaccinated adults. It has a global distribution, but is largely eradicated in developed countries due to vaccination. All monkeys and apes are susceptible, with high morbidity and mortality ranging from 0% to 100% depending on the species. Infection is via the respiratory route. The virus is trophic for dendritic cells, monocytes, and lymphocytes. Initial infection involves replication in both T and B lymphocytes with secondary infection of dendritic cells followed by epithelia and nervous system (de Vries et al., 2012). Affected epithelia include the upper and lower respiratory tract, skin and GI tract. Due to lympholysis, measles virus causes profound immune suppression causing secondary viral and bacterial infections. Death is usually due to diarrhea or pneumonia. Occasionally central nervous system (CNS) infection can be a late sequela.

Although apes are presumed to be susceptible to measles infection and vaccination is recommended, there are few published reports of the clinical or pathological signs in these species. A wide-reaching respiratory disease outbreak in wild mountain gorillas in Rwanda in 1988 is presumed to have been due to measles and secondary mycoplasma pneumonia, based on rising serologic titers and histological findings (Hastings et al., 1991). Although a characteristic rash, facial edema and chemosis are common in OW monkeys, none was seen in gorillas. Lung lesions are of typical bronchointerstitial pneumonia, centered on small bronchi and bronchioles with necrosis of epithelium and filling of lumena by mucus and cell debris. The lesion extends into the interstitium as acute alveolar damage with exudation of protein rich edema fluid, increased numbers of alveolar macrophages, and sloughed cellular debris. Syncytia are present in the parenchyma or airways (giant cell interstitial pneumonia), and air sac epithelium (Fig. 15.22). Both intranuclear and intracytoplasmic inclusion bodies are seen in syncytia and other cells. Lymphoid depletion with germinal center syncytia (Warthin-Finkeldy cells) may be seen.

Parainfluenza viruses types 1, 2, and **3 (HPIV-1, HPIV-2,HPIV-3,** respectively) (genera *Respirovirus* and *Rubulavirus*) are the most prevalent and significant of the human parainfluenza viruses. HPIV-1 and 2 are often associated with laryngotracheitis, while HPIV-3 is often associated with bronchitis and bronchiolitis. HPMV-1 infects chimpanzees and replicates in lower airway epithelium (Skiadopoulos et al., 2002). Disease varies from asymptomatic with virus replication and sheading, to fatal pneumonia in infant chimpanzees. Histologically, PMV-1 may form large multinucleated syncytia in respiratory epithelium. Gibbons are susceptible to spontaneous infection with PMV-3 (synonymous with PIV-3) occurring as respiratory disease outbreaks (Martin and Kaye, 1983). Mortality is not reported. As is the case for many of the respiratory viruses, PIV infections are often complicated by bacterial pneumonia (Jones et al., 1984).

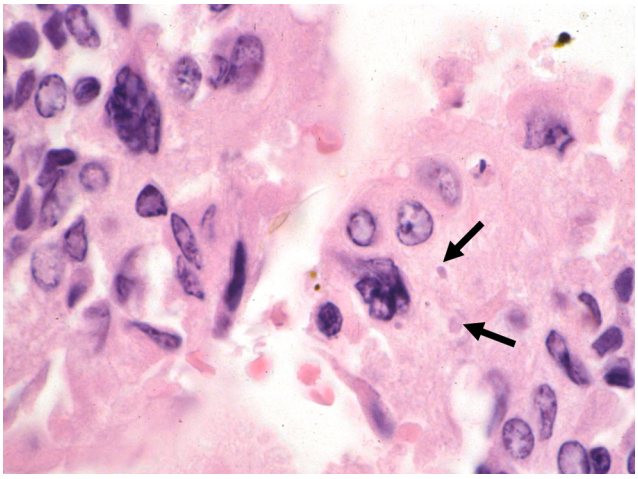

FIGURE 15.22 Viral airsacculitis in a mountain gorilla. Syncytia containing both intranuclear and intracytoplasmic inclusion bodies *(arrows)*. Electron microscopy confirmed paramyxoviral nucleocapsids suggestive of measles virus infection.

Mumps virus, a *Rubulavirus* related to HPIV-2, causes "mumps"; humans are the natural host. It is a self-limiting, respiratory disease seen primarily in children. The typical childhood disease consists of fever, aches and pains, sore throat and parotid gland inflammation that causes swelling of the face and angle of the jaw (Rubin et al., 2015). Respiratory signs are also present because the respiratory tract is the portal of entry. Infection of the CNS occurs commonly but is largely asymptomatic, though aseptic meningitis can occur. Orchitis is common in puberal and adult males. Antibodies against mumps virus are detected in gorillas and chimpanzees (Wright et al., 1982). Natural disease in chimpanzees mimics the childhood syndrome with sialoadenitis (parotiditis), and pharyngeal and palatine erosions. Histologically there is interstitial and periglandular edema with perivascular and interstitial mononuclear cell inflammation and necrosis of acinar and ductal epithelium. Post infection scarring of the parotid gland may occur. Mumps virus causes syncytia formation in tissue culture, but syncytia are not reported in clinical cases (http://virology-online.com/viruses/MUMPS3.htm).

Influenza viruses, (family *Orthomyxoviridae*; genus *Influenzavirus*) including **Influenza A** and **B,** have a broad host range with avian, swine, equine, canine and human (primate) strains; genetic recombination causes shifts in host range. Antibodies to influenza A and Influenza B are common in serosurveys of apes in captivity and in the wild (Buitendijk et al., 2014; Kalter and Heberling, 1978; Kalter et al., 1997; Whittier, 2010), and chimpanzees can be infected experimentally. Susceptibility to different strains depends on sialic acid cell surface receptors in the upper and lower respiratory tract and the surface proteins of the virus (Gagneux et al., 2003). There is debate about the infectivity of human influenza viruses in nonhuman primates in general (Davis et al., 1992); however, illness is often reported in ape collections at times when "flu" is circulating in the human population. Flu-like disease can be caused by a variety of respiratory viruses and serology or virus detection should be used to confirm the causative etiology (Hanamura et al., 2008). Morbidity in colony-housed gibbons infected with influenza A2 Hong Kong 68 included both respiratory and gastrointestinal signs (e.g., lethargy, anorexia, serous to mucous nasal discharge, cough, and diarrhea or constipation) (Johnsen et al., 1971). The gross lesion in gibbons is pneumonia, most severe in caudal lobes, with consolidation and hemorrhage. Fibrinous bronchointerstitial pneumonia is seen histologically with epithelial necrosis and sloughing in terminal bronchioles and filling of alveoli by fibrin, edema, erythrocytes, and macrophages. Bronchiolitis obliterans may be present focally. Secondary bacterial infections result in superimposed, suppurative bronchopneumonia. The absence of syncytia or inclusion bodies and presence of severe alveolar hemorrhage may help to differentiate "flu" from other fatal respiratory infections.

Picornaviruses

Encephalomyocarditis virus (EMCV; genus *Cardiovirus*) was first isolated from a gibbon in captivity in Florida that died of congestive heart failure. The virus occurs in many regions of the world, but with discontinuous distribution. In the United States, natural infections in zoo animals are much more common in the southeast and south (http://www.cfsph.iastate.edu/pdf/shic-factsheet-encephalomyocarditis-virus). Reservoir hosts are rodents, but the virus has broad host range including nonhuman primates, swine, carnivores, elephants and other exotic hoofstock. The transmission route is orally from food or water contaminated by infected rodent feces, and from ingestion of raw meat from an infected animal. The virus has broad tissue tropism but clinical signs are attributable to viral damage to beta cells of the pancreatic islets (causing type I diabetes, primarily in rodent models), myocardial fibers causing myocarditis, and infection of CNS tissues causing meningoencephalitis and/or myelitis. Placental infection and fetal death may occur in nonhuman primates and swine. Although EMCV causes cell death, pathogenicity is linked to a strong host inflammatory response (Carocci and Bakkali-Kassimi, 2012).

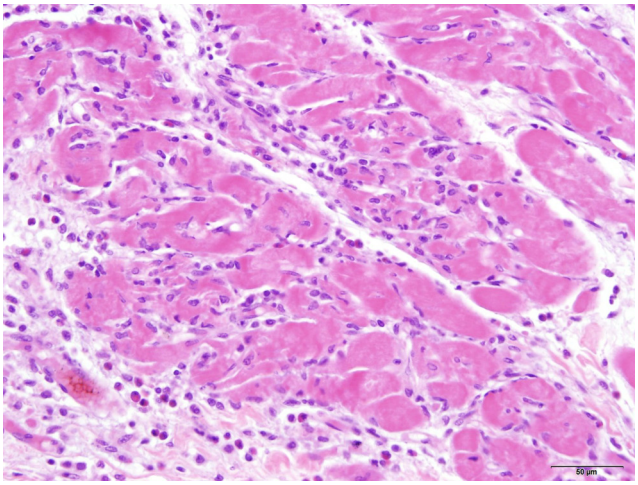

FIGURE 15.23 Encephalomyocarditis virus myocarditis infection in a bonobo. Characteristic myonecrosis, myophagia, interstitial edema, and mixed inflammation are seen in the heart.

Spontaneous disease can occurred in outbreaks in zoos and primate colonies (Canelli et al., 2010; Hubbard et al., 1992; Yeo et al., 2013). Affected species include lemurs, squirrel monkeys, baboons orangutans, chimpanzees, and bonobos (Jones et al., 2011; Reddacliff et al., 1997). Clinical signs associated with cardiac lesions include sudden death or congestive heart failure and pulmonary edema. Infected bonobos may present with coughing, mimicking respiratory virus infection. Placentitis and abortions have been reported in baboons. Gross lesions include pericardial effusion and severe pulmonary edema. Cardiomegaly and pale foci in the myocardium may be seen. Histologically, inflammation in the heart is lymphoplasmacytic and histiocytic, associated with myofiber degeneration and necrosis and variable amounts of hemorrhage. In affected bonobos, neutrophils may also be present (Fig. 15.23). Encephalitis, best described in squirrel monkeys, is characterized by cerebrocortical neutrophilic and lymphocytic inflammation with perivascular cuffing and loss of neurons in cerebral gray matter. Definitive diagnosis relies on virus detection by culture or PCR. There do not appear to be commercially available antibodies for immunohistochemistry or commercially available vaccines.

Enteroviruses

Humans are host to over 70 different **enteroviruses** and many others are found in cattle, swine, and nonhuman primates. These small, single stranded RNA viruses often have affinity for gastrointestinal and respiratory tracts, but also cause cutaneous, myocardial or nervous system lesions. Well known enteroviruses that have been reported in apes include **rhinoviruses** (common cold), **poliovirus,** and **coxsackieviruses**. The prevalence and effect of these viruses in apes have been incompletely explored. Studies in

free-living apes have shown that enterovirses can cocirculate in apes and humans (Harvala et al., 2014.)

Coxsackieviruses are divided into two groups, **Coxsackie A** and **B**, each with several serotypes. Positive serology is seen in several species of nonhuman primates including apes (Kilbourn et al., 2003). Deaths reported in apes include neonatal and adult chimpanzees infected with Coxsackie B5 and orangutans infected with Coxsackie B4 (Nielsen et al., 2012). Diarrhea and respiratory signs occur. Gross lesions include pneumonia, visceral congestion, and cardiac enlargement with pale streaking. Histologically, lymphocytic myocarditis consists primarily of CD3 positive T cells, along with occasional granulocytes, in the interstitium centered on necrotic myofibers. Meningitis and hepatic necrosis may also be seen. The lesions resemble those of EMCV infection and virus detection is needed to differentiate the two. Coxsackie virus infection may predispose to streptococcal pneumonia. Transmission is most often fecal oral. Infection of tonsils and regional lymph nodes results in secondary hematogenous spread to lungs, meninges, liver, and heart. Chronic intestinal carriage of coxsackieviruses has been noted in experimentally infected, clinically normal chimpanzees, raising concerns about zoonotic transmission (Melnick and Kaplan, 1953).

Poliomyelitis virus can affect all "simian" primates, but not prosimians. Humans are the primary host. The natural infection in apes is primarily a nonparalytic enteric disease with CNS involvement in less than 1% of cases (Douglas et al., 1970). After experimental infection, laboratory chimpanzees may be asymptomatic; however, natural infection in chimpanzees can lead to motor neuron signs including paresis and paralysis with secondary skeletal asymmetries (Morbeck et al., 1991; Williams et al., 2008). Poliovirus transmission is fecal-oral. Virus multiplies in the oropharynx and intestinal mucosa, spreads to lymphoid tissues (especially tonsils, cervical lymph nodes, gut-associated lymphoid tissue (GALT) and mesenteric lymph nodes), then becomes viremic leading to CNS infection. Fecal shedding may persist for months. Neurological lesions include nonsuppurative, polioencephalomyelitis with neuronal swelling, chromatolysis, neuron cell death, and neuronophagia. Inflammation is transiently neutrophilic becoming lymphocytic. Myelitis is centered on anterior (ventral) horns of the spinal cord and medulla. Occasional glial nodules are present in the motor cortex. Another **enterovirus, C99,** was implicated in acute flaccid paralysis resembling polio in a sanctuary-housed chimpanzee (Mombo et al., 2015).

Hepatitis viruses

Hepatitis A (HAV) (genus *Hepatovirus*), a picornavirus transmitted via fecal-oral routes is found worldwide. Humans are the probable natural host, but hepatitis A can be spread from human to primate, primate to primate, and primate to human, and there are nonhuman primate host-specific strains of HAV (Robertson, 2001). Serological evidence of natural infection can be found in zoo-housed gibbons, chimpanzees, orangutans and gorillas (Sa-nguanmoo et al., 2010). Chimpanzees can be infected experimentally (Popper et al., 1980). Spontaneous infection is usually subclinical, detected only with clinical chemistry, but fatal infections can occur. Acute lesions in chimpanzees consist of multifocal, predominately periportal, individual hepatocyte necrosis, and acidophilic bodies with moderate lymphocytic inflammation accompanied by mononuclear periportal hepatitis that breaches the limiting plate and bridges between portal areas. Lesions typically resolve in less than a month. Liver enzymes especially SGPT (ALT) increases dramatically but transiently. HAV does not establish persistent infections.

Hepatitis B (**HBV**; family *Hepadnaviridae*; genus *Orthohepadnavirus*) occurs worldwide in humans and produces chronic active infections leading to cirrhosis and hepatocellular carcinoma. Human hepadnaviruses are used experimentally to infect chimpanzees as a model for HBV vaccine development. Nonhuman primate HBV strains also exist in gibbons, orangutans, gorillas and chimpanzees in captivity and in the wild (Bonvicino et al., 2014). The prevalence of HBV exposure and chronic infection in chimpanzees in the US zoos is about 2%, and must be taken into account in management decisions (Meals et al., 2016). Ape to ape transmission can occur within and between species. The zoonotic potential of ape HBVs is unclear; however, there is documented transmission between a zoo-housed gorilla and a keeper. In apes, acute HBV infections are usually subclinical. Histologically, there is diffuse, panlobular "activation" of sinusoidal lining cells and multifocal random individual hepatocyte necrosis (sometimes becoming confluent) with a few attendant lymphocytes. Acidophilic hepatocytes and multinucleated hepatocytes may be present, and elevation of liver enzymes, especially SGOT (AST), is seen. Histological lesions in chronic HBV carrier chimpanzees consist of marked lymphocytic periportal hepatitis without disruption of the limiting plate, and scattered "ground glass" hepatocytes in which HBsAG can be demonstrated by immunohistochemistry (Thung et al., 1981). Liver cancer and cirrhosis, common in humans, are not usual sequela in chimpanzees (Porter et al., 2004).

Filoviruses (Hemorrhagic Fever Viruses)

African Ebola viruses (genus *Ebolavirus*; family *Filoviridae*) are OIE listed reportable, zoonotic viruses that are highly pathogenic for humans, apes and other primates. Of the five recognized subtypes of African Ebola, three have been associated with outbreaks: Ebola Zaire, Ebola Sudan, and Ebola Bundigbugyo. Bats are suspected, but not proven reservoir hosts. Devastating outbreaks of African Ebola with population effects occur in chimpanzees, bonobos and western lowland gorillas in equatorial Africa (Walsh et al., 2003; Leroy et al., 2004a). Transmission is through direct contact with blood or other secretions from infected individuals, or ingestion of infected tissues. Experimental

disease (rhesus and cynomolgus macaques) consists of a 2–6 day incubation period, early fever and petechial rash (in rhesus), depression, dyspnea, diarrhea, blood from the rectum and vagina, lymphopenia, and thrombocytopenia. Gross lesions include hemorrhage in the skin, lungs, liver, and spleen, splenomegaly, and interstitial pneumonia. Histologically, hemorrhage, hepatic lipidosis, hepatic necrosis with basophilic cytoplasmic inclusions, and lymphoid necrosis are reported in humans and experimentally infected primates. Macrophages are infected and inflammation is often lymphocytic and histiocytic. In the only description of naturally occurring Ebola in a chimpanzee, gross lesions suggestive of "hemorrhagic septicemia" were seen (Wyers et al., 1999). Liver lesions include multifocal hepatitis, multinucleated hepatocytes throughout the parenchyma, and Kupffer cell hyperplasia. Eosinophilic intracytoplasmic inclusion bodies are seen in Kupffer cells but not hepatocytes. Lymphoid depletion with lymphocytolysis and hemorrhage is seen in the spleen along with "fibrinoid necrosis" in red pulp, especially in the marginal zones of the periarteriolar lymphoid sheaths. Splenic macrophages contain cytoplasmic inclusions, similar to those in the Kupffer cells. The presence of Ebola virus is confirmed with immunohistochemistry. Serological studies suggest some apes survive exposure to Ebola viruses (Leroy et al., 2004b).

Retroviruses

Many **exogenous retroviruses** (family *Retroviridae*) have been identified in apes. These include the gibbon ape leukemia virus (GALV, genus *Gammaretrovirus*), primate T lymphotropic viruses (PTLVs; genus *Deltaretrovirus*), simian immunodeficiency viruses (SIVs, genus *Lentivirus*) and foamy viruses (genus *Spumavirus*) (Peeters and Delaporte, 2012). Most of these are homologous to human retroviruses and cross species transmission has occurred historically and in recent times. Some appear to be apathogenic (e.g., foamy viruses). All the retroviruses have the propensity to cause chronic infections with integration of DNA provirus into the host genome. Some are oncogenic.

Gibbon ape leukemia virus (GALV) of gibbons has historically been associated with outbreaks or hemolymphatic malignancies in individuals (Kawakami et al., 1980). Virus is shed in the urine and feces, although the mode of transmission is uncertain. Antibodies against GALV can be identified in gibbons without evidence of disease (Siegal-Willott et al., 2015), but both natural and experimental infection can result in disease. Because GALV lacks viral oncogenes, latency may be prolonged and pathology variable depending on when and where proviral integration occurs. Accordingly, age at onset of illness varies, and disease course can be prolonged (up to 3 years). Conditions associated with GALV infection include malignant lymphoma, lymphoblastic leukemia, myelogenous (granulocytic) leukemia and "osteopetrosis" of long bones. In cases of granulocytic leukemia there is marked circulating granulocytosis with infiltration of bone marrow, liver, lymph nodes, and spleen. Infiltrated tissues often have a greenish hue (chlorosis). Disease due to GALV is no longer prevalent in the US SSP populations of gibbons, and although antibodies are still present in some apes, it is thought that this disease may no longer be of concern (Brown and Tarlington, 2017).

Simian immunodeficiency viruses (SIVcpz, SIVgor) (genus *Lentivirus*) occurs in a variety of nonhuman primates, including chimpanzees and western lowland gorillas, but not (to date) in free-ranging eastern lowland and mountain gorillas, bonobos, gibbons, or orangutans (Ayouba et al., 2013; Li et al., 2012; Warren et al., 1998). Two strains of SIVcpz exist, SIVcpz*Ptt* infecting the central chimpanzee subspecies and SIVcpz*Pts* infecting the eastern chimpanzee. Wild chimpanzees of the other two subspecies do not appear to be naturally infected. SIVgor appears to have arisen from cross-species transmission of SIVcpz-*Ptt* (Etienne et al., 2012). Cross-species transmission of SIVcpz*Ptt* into humans is likely the origin of HIV-1 strains in phylogenetic Group M, the strain associated with the AIDS pandemic, as well as strains in Group N. In contrast, SIVgor appears to be the origin of HIV-1 Group O and P strains (D'arc et al., 2015). Vertical transmission has been demonstrated for SIVcpz and SIVgor and horizontal transmission proven for SIVcpz and suspected for SIVgor (Rudicel et al., 2010). Population wide studies indicated negative effects on population growth, survival, and reproduction in free-ranging eastern chimpanzees with SIVcpz.

Pathologic changes are reported in SIVcpz*Pts* and SIVcpz*Ptt* infected eastern chimpanzees (Etienne et al., 2011; Terio et al., 2011). Significantly lower numbers of CD4+ lymphocytes are present in lymphoid tissues in comparison with controls, and in some chimpanzees, CD4+ T cell loss is selective (other lymphocyte populations remained intact). Marked depletion of cortical

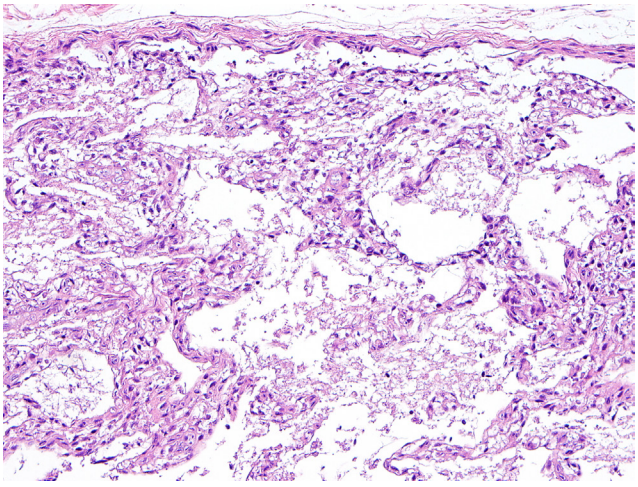

FIGURE 15.24 Natural SIVcpz infection in a chimpanzee. Infection is associated with marked lymphoid depletion that results in a "cobweb" appearance in the lymph nodes. *(Photo Courtesy of Gombe Ecohealth Program)*

and paracortical T and B lymphocytes in lymph nodes (Fig. 15.24) and marked lymphoid depletion in the spleen consistent with end-stage infection or AIDS-like disease may be seen. At death, chimpanzees may be emaciated with profound sarcopenia and hepatocellular atrophy. In all infected chimpanzees, hyaline deposits within splenic periarteriolar lymphoid sheaths, a nonspecific marker for chronic immune activation, is noted with severity paralleling the loss of lymphocytes. To date, SIVcpz*Pts* infections have not been associated with malignancies. Opportunistic infections likely occur, but are difficult to prove due to rapid decomposition in apes found dead in the wild. Decreased peripheral blood CD4+ T cell count has been described in a sanctuary-housed SIVcpz*Ptt* infected chimpanzee with frequent infections with a various pathogens.

Bacteria

Streptococcus pneumoniae (Diplococcus, Pneumococcus), a Gram-positive, diplococcal bacterium, is a common cause of pneumonia, meningitis and pericarditis in apes; vaccination is recommended. Predisposing factors include young age, immune suppression, and underlying viral infections, such as parainfluenza-3, human metapneumovirus, and human respiratory syncytial virus. Reports include pneumonia and meningitis in a juvenile wild chimpanzee, meningitis in chimpanzees and gorillas, respiratory disease including sinusitis and air sacculitis in gibbons, bonobos, lowland gorillas and orangutans, and tonsillitis in a captive gorilla (Solleveld et al., 1984; Unwin et al., 2013; van der Linden et al., 2009). Numerous strain and serotypes of *S. pneumoniae* have been described in humans and animals. In many cases, strain types of *S. pneumoniae* recovered from captive apes are similar to those identified in their human caretakers (Szentiks et al., 2009), raising the concern for anthropozoonotic and zoonotic transmission. Although nasopharyngeal carriage of *S. pneumoniae* occurs commonly in humans it is not thought to be a natural pharyngeal inhabitant in other primates. Some research suggests that ape specific strains may exist, but the extent to which strain type is associated with pathogenicity remains uncertain (Chi et al., 2007).

Gross pulmonary lesions include suppurative bronchopneumonia and or pleuropneumonia (Fig. 15.25A) with fibrinous adhesions in the thoracic cavity. There may be abscesses within the lung and thoracic cavity and inflammation may efface large areas of pulmonary parenchyma. Histologically, lesions contain numerous degenerate neutrophils, fibrin, fewer macrophages and intra- and extracellular Gram-positive cocci, which can be identified antimortem by bronchoalveolar lavage (Fig. 15.25B). In cases with pleuritis or pericarditis, similar inflammation coats the diaphragm, thoracic wall and pericardium. While some reports mention an interstitial component, this may be due to viral co-infection rather than the bacteria alone.

Klebsiella pneumoniae is also often a component of ape respiratory disease, including airsacculitis and pneumonia. Although it can be a primary pathogen, especially if it carries the hypermucoviscosity genotype, it is often secondary to viral infections or is a coinfection with *P. pneumoniae*. The capsule of *Klebsiella* can inhibit neutrophil chemotaxis and phagocytosis and, although pyogenic, flooding of alveoli with activated macrophages is common. **Pasteurella multocida** is also associated with pneumonia and air sacculitis (Köndgen et al., 2011).

Bacterial meningitis is a sequel to streptococcal and other pneumonias, especially in infant apes (Solleveld et al., 1984). It is characterized by dull white to yellow meninges with exudates present in sulci and pooling at the base of the brain around the pituitary. In some cases,

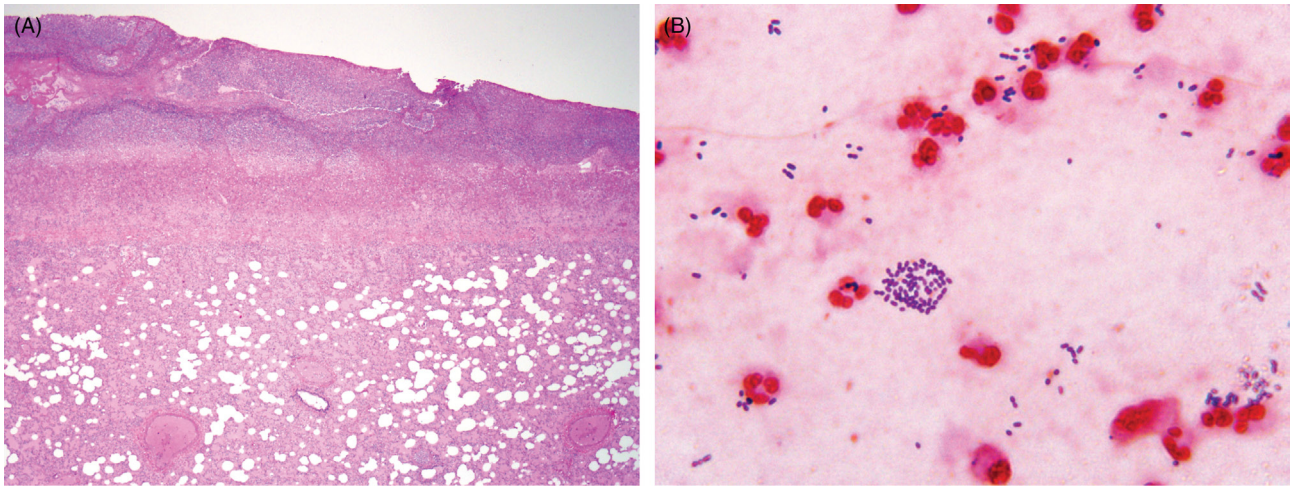

FIGURE 15.25 Suppurative pleuropneumonia due to *Streptococcus pneumoniae* in a chimpanzee (A) and gorilla (B). (A) The pleural is markedly thickened by fibrin and neutrophils *(top of image)* and there is consolidation of the underlying lung parenchyma. (B) Typical Gram-positive diplococci can be seen in bronchoalveolar lavage cytology. *(Part A : Photo Courtesy of Gombe Ecohealth Program)*

meningeal vessels are congested and the meninges reddened. Histologically, there are dense infiltrates of degenerate neutrophils within the leptomeninges, ventricles and extending into the parenchyma. Gram positive cocci are seen in most cases. Macrophages, some with intracytoplasmic cocci, and lymphocytes may be present depending on the chronicity of infection. Necrotizing vasculitis and fibrin thrombi are common. Most reported cases of meningitis also have pneumonia, suggesting the respiratory tract as the primary site of infection.

Initial diagnosis can be based on cytology (bacterial morphology in exudates) and gross or histologic findings, but confirmation requires culture or molecular detection. Multi-locus strain typing of *S. pneumoniae* can provide additional information on molecular epidemiology. As many cases have concurrent viral infections, evaluation for common viral respiratory viruses is warranted.

Meningitis in apes can also be caused by the Gram positive coccus **Staphylococcus aureus**. Most cases appear to arise from opportunistic infection of wounds and septicemic spread to the brain or extension from otitis. Lesions in the brain are similar to those described for *S. pneumonia,* but encephalitis with regional necrosis and gliosis appears to be more common with *S. aureus*. Other bacterial causes of meningitis in apes include **Klebsiella pneumoniae** and **Proteus mirabilis** (Iverson and Popp, 1978).

Staphylococcus aureus strains can be shared between humans and chimpanzees in sanctuary settings and **methicillin resistant staph aureus (MRSA)** can be carried by chimpanzees in managed colonies (Hanley et al., 2015). Suppurative arthritis due to *S. aureus* has been reported in a single neonatal orangutan (Hoopes et al., 1978).

The ape air sacs arise from the lateral saccules of the larynx (Fig. 15.26A). Gibbons, chimpanzees and gorillas, but not orangutans, also have a small midline hyoid air sac associated with a hyoid body intraosseous bulla (Steele et al., 2013). Not all gibbons have well developed air sacs, but the siamang has a highly distensible central "gular sac" that blows up like a balloon during vocalization. Air sacs are large in both chimpanzees and bonobos, but are more voluminous in gorillas and orangutans, extending ventrally under the clavicles into the axilla and dorsally around the neck. Air sac lining epithelium is generally ciliated ranging from cuboidal to stratified or pseudostratified (Fig. 15.26B). Air sacs develop gradually postnatally.

Airsacculitis has been described in all of the apes. It is most common and severe in orangutans, possibly due to the extensive and pendulous nature of the ventral "throat sac" and the extensive associated fat pad causing traction on the air sac. Disease occurs in all age groups (Kumar et al., 2012; Steinmetz and Zimmermann, 2011). Prevalence seems to be increased in males, hand-reared apes, and Bornean (vs. Sumatran) orangutans. Affected orangutans are more often related to others with respiratory disease than to healthy individuals, suggesting a possible genetic component. In chimpanzees, some studies have found equal sex distribution while others (confounded by a larger male population) noted a possible male bias. In all species, the most common presenting signs include cough, halitosis, and purulent nasal discharge. A variety of Gram-negative and Gram-positive bacteria are identified, often as mixed infections with *Pseudomonas aeruginosa* the most reported isolate. Viral respiratory infection may predispose to infection.

Gross and histologic lesions are similar across species. Exudate can be present bilaterally or unilaterally and distension of the air sacs may be seen externally. Exudate varies from pale to dark tan to yellow and is often viscous (Fig. 15.27A). Air sac walls are thickened and opaque in more severe chronic cases and septation and compartmentalization may develop due to fibrosis. Histologically, the air sac epithelium is thickened with loss of cilia and squamous metaplasia (Fig. 15.27B). The subepithelial stroma is thickened by edema or fibrosis with variable inflammation including formation of lymphoid

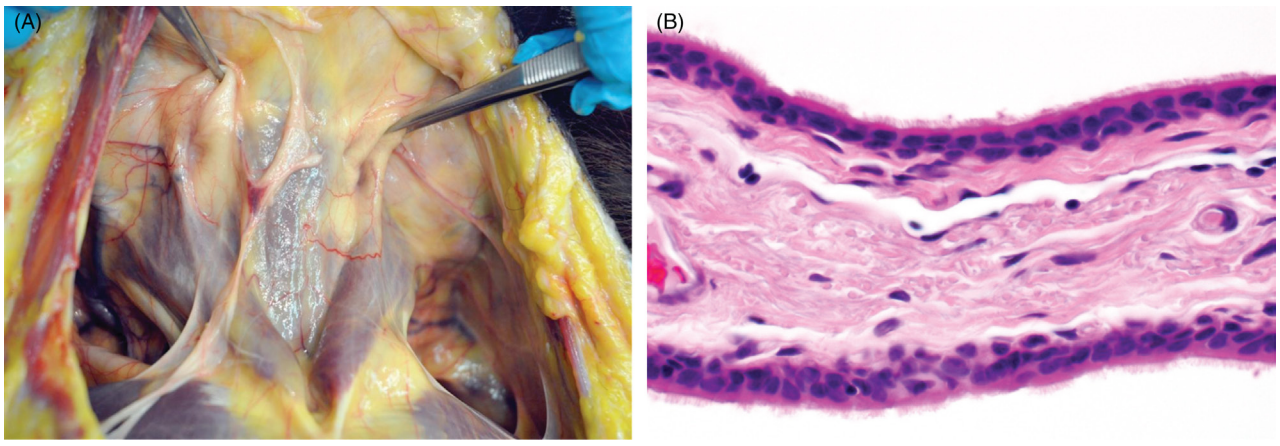

FIGURE 15.26 (A) Normal air sacs and ostia (held open by forceps) in an orangutan. Note the abundant fat in retract skin. (B) Normal air sacs are lined by cuboidal to low columnar, pseudostratified, ciliated epithelium.

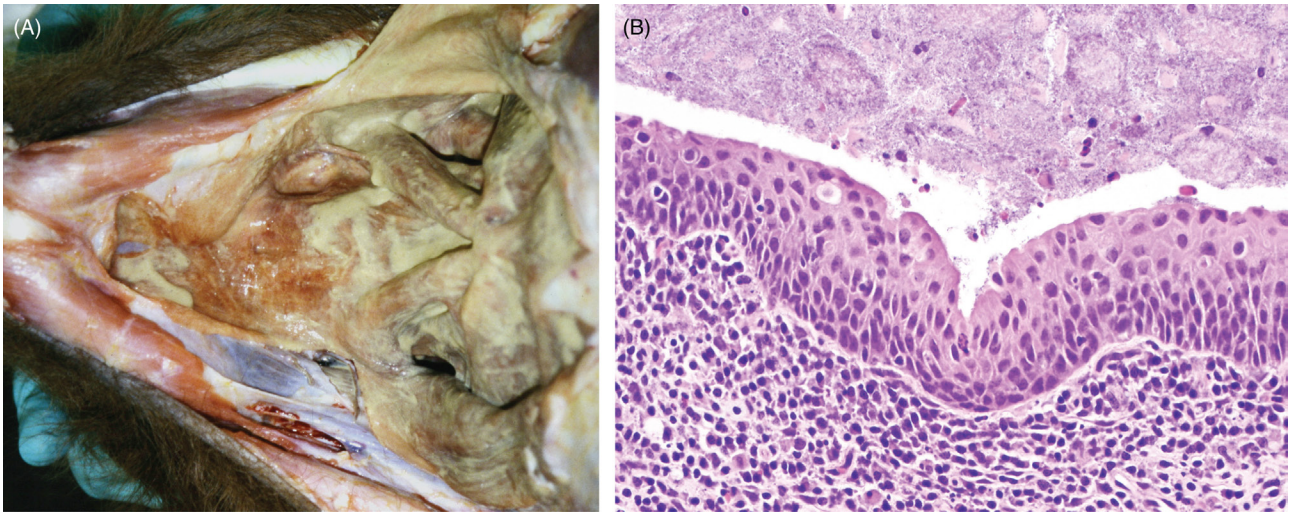

FIGURE 15.27 Severe chronic airsacculitis in an orangutan. (A) There is thickening and opacification of the air sacs and accumulation of a tan exudate. (B) The air sac epithelium is markedly thickened and has undergone squamous metaplasia. Subjacent, dense lymphoplasmacytic inflammation is present and a luminal exudate consists primarily of bacteria and necrotic cellular debris with occasional intact neutrophils.

follicles. Aspiration of purulent material and secondary bronchopneumonia occurs. Sinusitis may also be present and is postulated to contribute to the pathogenesis of air sac infections (Steinmetz and Zimmermann, 2011).

Apes have ethmoid, sphenoid, frontal and maxillary sinuses, of which the maxillary sinuses are generally the largest (Koppe and Ohkawa, 1999; Preuschoft et al., 2002). **Sinusitis** is reported in all apes. The use of MRI and CT has enhanced our understanding of the three dimensional anatomy of the sinuses and their role in respiratory disease. The maxillary sinus surrounds the roots of the "cheek teeth" in gibbons, chimpanzees and gorillas (but not orangutans) and dental disease may cause sinusitis in these species.

Periodontal disease is common in captive apes and is also seen in free-living individuals especially gorillas and chimpanzees (Lowenstine et al., 2016) (Fig. 15.28). As in other species, dental plaque or calculus and a variety of anaerobic oral bacteria are implicated. The teeth of wild apes are often black, either from diet or melanogenic oral bacteria (Muhangi, 2008). Potential complications include alveolar bone resorption, osteomyelitis, and vegetative endocarditis.

Intrabdominal and retroperitoneal abscesses are reported to be frequent in gorillas; there are single case reports of the latter in an orangutan, a subadult female chimpanzee, and a juvenile male chimpanzee (Hahn et al., 2014). In one study 8.5% of captive western lowland gorillas had suspected intraabdominal abscesses of which 90% were mostly in overweight, reproductively inactive adult females. Affected animals are often lethargic and anorexic with recto-genital discharge and constipation. Abdominal distension is noted in some cases. Abscesses typically occur in the caudal abdomen and intrapelvic region and can involve the perirenal retroperitoneum and

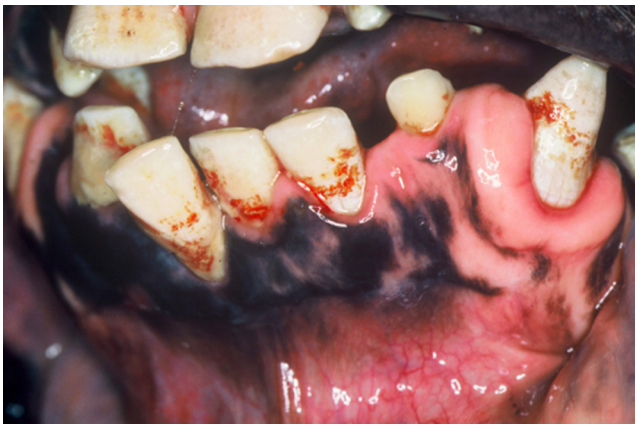

FIGURE 15.28 Periodontal disease and stomatitis in an orangutan. Both severe gingival regression and proliferation of the gingival mucosa are seen. *(Photo Courtesy of L. Braswell and Zoo Atlanta)*

abaxial muscles. Lumbar, perirectal or perivaginal fistulas may develop. Extenive fibrous adhesions are common regionally among the reproductive, distal gastrointestinal and urinary tracts, often making it difficult to discern their origin. Gastrointestinal perforation or appendicitis is often suspected. As female gorillas are disproportionately affected, a reproductive tract origin is also plausible. A variety of bacteria are been isolated including *Escherichia coli, Morganella morganii, Fusobacterium necrophorum, Klebsiella pneumoniae,* hemolytic *Streptococcus* and *Staphylococcus* spp., *Bacteriodes* sp., *Enterococcus* sp., *Hemophilus* sp., *Proteus* sp., and *Actinomyces* sp. Note that **intraabdominal adhesions** are common in all wild and captive adult apes, even in the absence of overt peritonitis.

Bacterial enterocolitis is common in apes, often presenting as diarrhea with lethargy and anorexia sometimes

culminating in death (Meehan and Lowenstine, 1994). While the majority of cases of ape enteritis are attributed to bacteria, such as **Salmonella spp., Yersinia spp**., **Campylobacter spp. and Shigella spp.,** parasitic and viral causes must also be considered (though the latter are less well documented). *Campylobacter*, *Salmonella*, and *Shigella* spp. have all be identified in free-ranging, human-habituated mountain gorillas, primarily in sub- and young adults, frequently in the absence of diarrhea (Nizeyi et al., 2001). *Shigella* spp., primarily *flexneri*, are common isolates from clinical cases of diarrhea in zoo-housed apes (Banish et al., 1993). Transmission is fecal-oral. In gibbons, persistent infection with periodic shedding of *S. flexneri* complicates eradication. Lesions of shigellosis in apes have not been well described but are expected to be similar to those noted in monkeys (i.e., colonic dysentery). Diagnosis is based on culture and or PCR. *Salmonella* spp. can cause acute hemorrhagic enterocolitis with septicemia especially in young, aged or immunocompromised individuals (Paixão et al., 2014). Both *Campylobacter coli* and *C. jejuni* can be isolated from apes with diarrhea (Pazzaglia et al., 1994). Natural infection with *Helicobacter* spp. is reported but pathogenicity is not documented (Flahou et al., 2014).

Mycobacterial infections can occur in any ape and all are susceptible to ***Mycobacterium tuberculosis* (Mtb)** and other members of the Mtb complex, for example, ***M. bovis,*** and ***M. africanum*** (Coscolla et al., 2013; Stephens et al., 2013; Wilson et al., 1984). Humans are the main hosts of Mtb; transmission is by aerosolization or through fomites contaminated with human sputum and exudates. Oral infection can occur, especially in infant apes fed unpasteurized milk from cows or goats. The source of infection is not always evident, but transmission from caretakers, visitors, conspecifics, or other animals in a collection are described. In early days of ape zoo-keeping, this was one of the most common causes of mortality. When glass- fronted enclosures separate apes from human visitors, the incidence of tuberculosis (TB) in apes drops precipitously. At the Philadelphia Zoo, 43% of 7 ape deaths from 1901 to 1920 were due to TB, while from 1921 to 1975 only 11% of 98 apes necropsied had TB (most occurring early in the time period) (Snyder, 1978). Chimpanzees held in research facilities have been infected, but apes (especially orangutans) kept as pets, confiscated from illegal ownership, and housed in sanctuaries or rehabilitation centers with close human contact, are at especially high risk http://www.thejakartapost.com/news/2011/11/24/tuberculosis-strikes-orangutans-sanctuary.html.

Mtb is considered one of the greatest reverse zoonotic health concerns for human-habituated wild ape populations (Gilardi et al., 2015). Fortunately, no cases have been identified during 30 years of necropsies of habituated wild mountain gorillas or by necropsy or PCR-based screening over the past 10 years in the well-studied chimpanzees of Gombe (Terio et al., 2011; Wolf et al., 2016). However, a wild chimpanzee from Côte d'Ivoire, killed by a leopard, was determined to be infected with *Mycobacterium africanum* (Coscolla et al., 2013).

Apes with tuberculosis may have anorexia, weight loss and respiratory signs, such as dyspnea and cough. The lungs are the primary site of infection with drainage to local lymph nodes and systemic spread to the liver, spleen, kidney, and other organs in advanced cases. At necropsy, lesions are similar among the *M. tuberculosis* complex bacteria (e.g., *M. bovis*) and to those noted in OW monkeys (see Chapter 14). When the route of bacterial transmission is respiratory; lesions consist of multifocal to coalescing granulomatous pneumonia with multinucleated cells and varying degrees of central caseation and mineralization. Air sac involvement has been described in orangutans with concurrent lung lesions. Oral infections can result in widespread granulomatous inflammation in abdominal viscera. Both intrahistiocytic and extracellular acid fast positive bacilli can be identified in lesions, but infections are commonly paucimicrobial.

Post mortem diagnosis is based on the characteristic lesions, presence of acid-fast positive bacilli and, ideally, microbiological or genetic characterization. Tuberculin skin tests are not always reliable for ante mortem diagnsosis as these tests can be falsely negative due to stage of disease (both early or advanced tuberculosis) and overall immune function (Dench et al., 2015). False positive results occur due to cross-reaction with environmental nontuberculous *Mycobacterium* spp. (especially in orangutans) or vaccine adjuvant (in vaccinated animals). Serologic tests are unreliable for identifying latent disease. A gamma-interferon stimulation assay has been developed for use in nonhuman primates, but multiple tests may be necessary for definitive antemortem diagnosis (Lerche et al., 2008).

Nontuberculous mycobacteria, including the ***M. avium complex*** organisms, can also infect apes. As in monkeys, underlying immune suppression should be suspected. These organisms are often environmental and can be found in municipal tap water. Histiocytic enteritis, resembling Johne's disease of cattle, is one manifestation as reported in a siamang gibbon (Munson et al., 1991).

Naturally occurring **leprosy** caused by ***Mycobacterium leprae*** can occur in chimpanzees, and gibbons are susceptible experimentally (Meyers et al., 1991; Waters et al., 1978). The organism cannot be cultured on artificial media, but can be detected in lesions and environmental samples using nucleic acid amplification. Transmission route in apes is unknown, but in humans, close contact, infected aerosols, environmental reservoirs, and traumatic inoculation are established routes (Bratschi et al., 2015). To date, all naturally occurring cases have been in wild or wild-caught chimpanzees and no cases have been reported in in-contact apes born in captivity. One difficulty in studying *M. leprae* infections is the prolonged latency

period and lack of accurate diagnostics for subclinical infections. Lesions can appear in captive chimpanzees decades after infection with organisms originating in country of capture (Suzuki et al., 2010). Lesions in apes are similar to those in humans and occur primarily on the face, ears and fingers. Early lesions are areas of cutaneous erosion that progress to coalescing dermal nodules. Histologically, the lesion are of the lepromatous, not tuberculoid, type, composed of activated macrophages/histiocytes with fewer lymphocytes, plasma cells and neutrophils. While inflammation can be diffuse, nodules characteristically surround deep dermal nerves and there is an overlying sub-epidermal zone lacking inflammatory cells (Hubbard et al., 1991; Leininger et al., 1980). Numerous acid-fast bacilli are present within histiocytes (multibacilllary) and in lower numbers in nerves. In a few cases, systemic spread of intrahistiocytic acid-fast bacilli has been noted. Some lesions are complicated by self-trauma. Diagnosis is based on the characteristic histological lesions. Bacteria stain more intensely with Fite-Faraco than Ziehl-Neelsen stains.

A condition similar to tertiary **yaws** in humans has been described in a population of wild western lowland gorillas in the Republic of Congo where human yaws is endemic (Leininger et al., 1980; Lovell et al., 2000). The disease is caused by the spirochete ***Treponema pallidum pertenue.*** In humans, tertiary yaws causes "gangosa" (syn. rhinopharyngitis mutilans) with severe destruction of the palate and nasopharynx, and "gondou," which is characterized by bony proliferation of the maxilla. In gorillas, 16% of apes in affected areas have severely disfiguring destructive facial lesions similar to gangosa; lesions also develop on the chest and shoulders with increasing age. Male gorillas are more affected than females, and affected males are less likely to be an alpha silverback. *T. p. pertenue* is transmitted by direct contact with infected lesions and by biting flies. Lesions suggestive of yaws osteitis have been seen in museum skeletons from chimpanzees and gorillas collected in West Africa, and gondou-like proliferative lesions on a gorilla skull are reported (Cousins, 2008). Histological lesions in apes are not described, but in humans the early skin lesions include localized acanthosis and spongiosis with intraepidermal pustules and spirochetes (demonstrated with silver stains or IHC using anti-*Treponema* antibodies) leading to ulceration (Mitjà et al., 2013). There is dense plasma cell infiltration in the dermis. Bone lesions are of proliferative periostitis.

Infection with ***Francisella tularensis,*** a Gram-negative coccobacillus, is reported in captive-held gibbons, orangutans, and a gorilla (Calle and Bowerman, 1993; Ketz-Riley et al., 2009). Both Type A (lagomorph associated) and Type B (rodent associated) strains are identified, which emphasizes the importance of rodent/lagomorph control in primate exhibits. Clinical signs are variable and similar to disease in other species. Pyogranulomatous inflammation in affected tissues (e.g., oral cavity, skin, lymph nodes, and lungs) and terminal bacteremia without inflammation are described. Diagnosis of tularemia requires identification of the bacteria. They are often poorly demonstrated with tissue Gram stains. PCR and immunohistochemistry are available ancillary diagnostic tests. Isolation can be complicated due to slow growth and culture overgrowth by concurrent bacteria or contaminants. *Francisella tularensis* is a Tier 1 Select Agent in the United States and is reportable to the Centers for Disease Control.

Anthrax-like disease is an important emerging cause of fatal disease in chimpanzees and gorillas in Africa and is an OIE listed reportable (Klee et al., 2010; Leendertz et al., 2006). Classical anthrax, caused by ***Bacillus anthracis*****,** affects a wide variety of animals and is frequent in African wildlife. The disease resembling anthrax in free-living African apes is caused by ***B. cerus*** **var. *anthracis.*** Affected apes present with sudden death or weakness and vomiting. Hemorrhage in multiple sites throughout the body, notably in the lung and intestines, is present at necropsy. Additionally, the lungs contain areas of edema and emphysema. Histologically, plump, Gram-positive bacilli are present intra- and extravascularly in all examined tissues, consistent with acute bacterial sepsis (Fig. 15.29). Extreme care should be taken during any necropsy investigation of possible anthrax in wild apes as Ebola occurs in similar geographic regions and is also associated with hemorrhage.

Chromobacterium violaceum**,** a motile, Gram-negative bacillus found in soil and water, produces pigmented purple colonies. It causes rare, often fatal, infections in humans and nonhuman primates. The portal of entry is through contaminated wounds or orally from contaminated water. The organism is endemic to tropical and subtropical areas

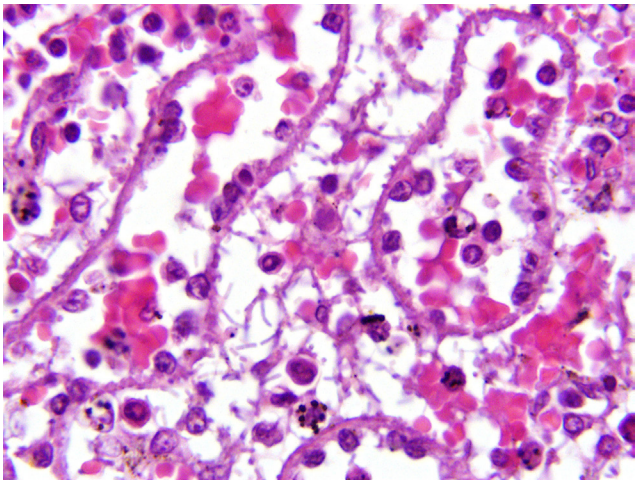

FIGURE 15.29 ***Anthrax*-like infection in a chimpanzee.** Myriad *Bacillus cereus* biovar *anthracis* bacilli are present in the splenic sinusoids. *(Photo Courtesy of the Taï Chimpanzee Project)*

in Asia, Africa, Australia and the Americas. Disease is reported in zoo and research colony gibbons in Malasia and Thailand, a guenon in Africa, and a howler monkey in Costa Rica. In the US, cases have occurred in colony-housed pigtailed and rhesus macaques and a baboon in Louisiana, and an Assamese macaque in Georgia (Groves et al., 1969; Liu et al., 2012). The most common gross lesions in gibbons are focal or multifocal hepatic and pulmonary abscesses suggesting septicemic infection. Skin ulceration or abrasion may, in some cases, represent the portal of entry. Abscesses are confirmed histologically, and encapsulation indicates chronicity. Small vessel thrombosis occurs in the lung adjacent to the abscesses.

Fungi

Dermatophytosis (ringworm) is occasionally reported in apes, including gibbons, gorillas, chimpanzees and orangutans in zoos and chimpanzees in sanctuaries and in the wild (Avni-Magen et al., 2008; Dubuis and Lucas, 2003; Nishida et al., 2007; Otcenasek et al., 1967). Lesions are variable including papular, crusting lesions on the face around the nostrils, focal or multifocal hair loss, and scaling of the skin over the entire body. Lesions may be puritic. Histologic lesions are similar to those in domestic animals with varying degrees of acanthosis and hyperkeratosis of the epidermis and hair follicles, and fungal elements in surface keratin, hair follicles and hair shafts. Differential diagnoses include dermatophilosis and ectoparasitism. Definitive diagnosis relies on culture; reported organisms include *Microsporum caninum*, *Micosporum gypseum*, *Trichophyton rubrum.*

Candidiasis due to ***Candida* spp.** is more common in zoo and free-living apes than is reported in the literature. Oroesophageal and tracheal candidiasis is reported in free-living and zoo-housed gorillas, chimpanzees and orangutans. Generalized disability, immune dysfunction, and antibiotic treatment are likely predisposing factors. Gross and histological mucous membrane lesions include plaques of hyperkeratosis with superficial ovoid yeasts and pseudohyphae oriented perpendicular to the epidermal layers causing retention of the statum corneum. A rare manifestation is focal nodular proliferation of the gastric mucosa as reported in a perinatal gibbon (Saëz, 1975). A candida-like yeast, associated with enteritis, diarrhea and dissemination with pneumonia reported in a juvenile white-handed gibbon, is the anamorph of ***Kazachstania heterogenica*,** an organism usually associated with the feces of rodents (Alvarez-Perez et al., 2012).

Geotrichosis due to ***Geotrichum candidum*** can be associated with outbreaks of watery diarrhea in zoo-house lowland gorillas ingesting contaminated produce (Dolensek et al., 1977). Conidia and hyphae of this yeast, identifiable by culture, are present in the feces.

Coccidioidomycosis, due to ***Coccidioides immitis*** or ***C. posadasii***, is a significant threat to captive chimpanzees and gorillas in endemic areas of the southwestern United States (Benirschke and Adams, 1980; Hoffman et al., 2007). These two species are separated by geography, cultural characteristics and molecular techniques. *C. immitis* is endemic to Mexico and the San Joaquin Valley of California, while *C. posadasii* is endemic elsewhere in California, Arizona, Texas, Mexico and South America. Infection is via inhalation of the small (<10 μm), air-borne, arthroconidia from saphrophytic hyphae in the soil. Once inhaled into the lungs, the conidia become larger spores or spherules that divide by endosporulation. Rupture leads to dissemination in the lungs and throughout the body by macrophage transport. Clinical signs include weight loss and cough. Lesions are typical of "valley fever" in other species and include focal, multifocal or diffuse pyogranulomatous pneumonia with characteristic spherules readily recognized by size (10–200 μm), thick, double-contoured refractile hyaline walls and endospores (2–4 μm). Dissemination to brain, eye, bone, and other locations frequently occurs. Hypertrophic osteoarthropathy can occur in infected chimpanzees. Antifungal therapy is sometimes successful if the diagnosis is made early enough.

Cyrptococcus neoformans and ***C. gattii*** cause **cryptococcosis**, a serious systemic infection that has been described in humans and a variety of domestic and wild animals including occasional reports in apes (Lester et al., 2011; Mischnik et al., 2004). *C. neoformans,* found worldwide, is thought to be mainly opportunistic, while *C. gattii,* found in tropical and subtropical area and the Pacific Northwest of North America, also infects immune competent hosts. Clinical signs described in a zoo-housed gorilla from Europe include marked weight loss, progressive lethargy and coughing followed by neurological signs of nystagmus, ataxia and tremor leading to euthanasia. Gross and histological lesions include cloudy meninges, cystic degeneration of periventricular white matter. Large numbers of cryptococcal spores surrounded by a thick, clear capsule are accompanied by predominantly nonsuppurative inflammation. The fungus is positive with silver stains; mucicarmine highlights the polysaccharide capsule.

Metazoa

Wild apes are hosts to a wide variety of parasites and there are numerous published accounts of coprological studies from all ape species. Correlation with clinical signs or lesions is rare, with the exception of gastritis (Muhangi 2008). A list of ape parasites can be viewed in Table e4 in the Supplemental Materials.

Pinworms indigenous to their natural hosts are found in wild gorillas, chimpanzees and orangutans (Nurcahyo et al., 2017). These parasites have a direct life cycle and live in

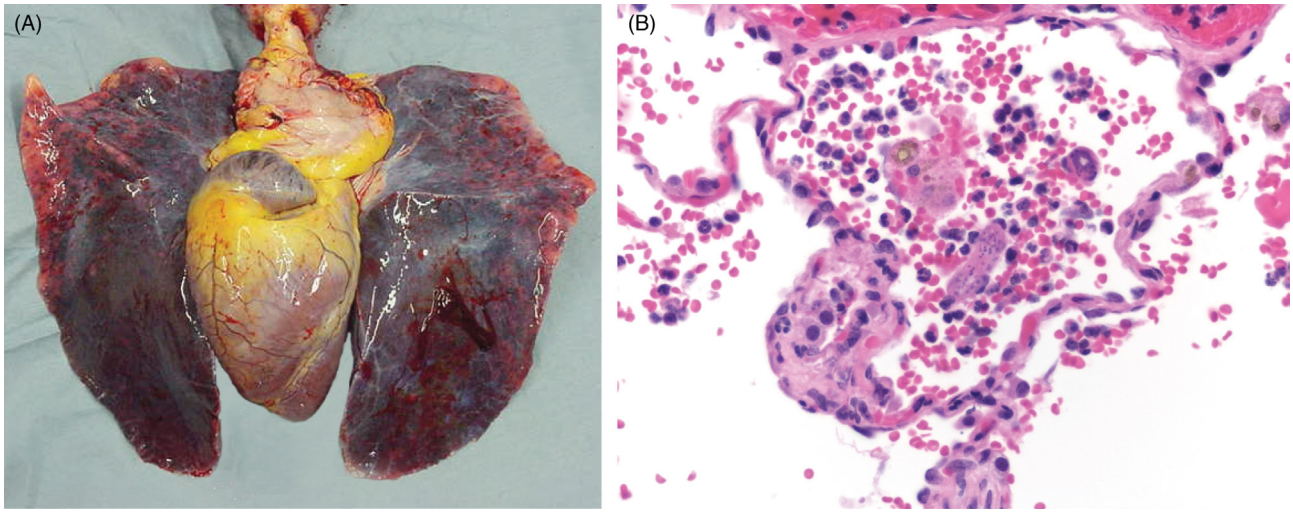

FIGURE 15.30 Pulmonary strongyloidiasis in an orangutan. (A) Infection and hemorrhagic pneumonia are associated with diffuse red discoloration and failure of the lungs to collapse. (B) Intraluminal larval nematodes are associated with hemorrhage and neutrophilic inflammation. *(Photos Courtesy of T. Schoeb, University of Alabama, Birmingham)*

the large intestine, including the vermiform appendix (which is present in all apes). Pinworm infections are usually subclinical; however, the human pinworm ***Enterobias vermicularis*** can be fatal in captive chimpanzees (Yaguchi et al., 2014). Gross lesions include colonic mucosal roughening and nodularity and draining tracks in the perianal skin. Histologically, *E. vermicularis* may be seen in the lumen of the ileum, cecum and colon, within nodules in the mucosa, in regional lymphatics, mesenteric lymph nodes, the liver and the lungs.

Strongyloidiasis an important, sometimes fatal disease of young apes in captivity and *Strongyloides* eggs or larvae are frequently identified in coprological studies of apes in captivity and in the wild (Benirschke and Adams, 1980; DePaoli and Johnsen, 1978; Lowenstine et al., 2008; Munson and Montali, 1990). Two species can parasitize hominids: ***Strongyloides fuelleborni*** (OW monkeys and apes natural hosts), and ***S. stercoralis*** (human natural host). Infection occurs when filariform larvae in the environment penetrate skin or mucous membranes, enter circulation, and travel through the heart to the lungs where they undergo further development in alveoli. Developing larvae are then coughed up, swallowed and penetrate the wall of small intestine where they develop into parthenogenic adult females that live in the crypts and produce eggs that are shed in the feces (*S. fuelleborni*) or hatch in the lumen to release larvae that are shed in the feces (*S. stercoralis*). Although infections are often asymptomatic, *S. stercoralis* can be associated with mortality due to hyperinfection in which larvae penetrate the colon wall instead of being shed in the feces (autoinfection), which results in heavy parasite loads. Ivermectin has reduced the incidence, but hyperinfection with *S. stercoralis* continues to be a cause of death in infant and juvenile orangutans. Clinical signs include cough, dyspnea, diarrhea or constipation, ileus, weight loss, and death. Gross lesion are often limited to pulmonary hemorrhage (Fig. 15.30A), but there may also be hemorrhagic or ulcerative enteritis and with mesenteric lymphadenopathy and pericarditis. Histologically, larvae can be seen in the lung where they are associated with acute interstitial pneumonia and multifocal mild to severe hemorrhage (Fig. 15.30B). They also may be found in the lumen, crypts, and intestinal lymphatics as well as in mesenteric lymph nodes. Adult worms are small and found in the intestinal glands/crypts (Fig. 15.31). Complications include toxemia/septicemia due to bacteria accompanying larval migration.

Esophagostomiasis, due to nodular worms (***Oesophagostomum* spp.**) is a common, sometimes clinically important, parasitic disease of apes, especially chimpanzees in range countries (Terio et al., 2018). ***O. stephanostomum*** is the species most often identified in chimpanzees and gorillas. ***O. bifurcum*** can also infect African apes, creating concern for zoonotic transmission (Krief et al., 2008). The worms live and cause lesions in the colon and adjacent mesentery. The life cycle is direct and there is no systemic migration. Ingested larvae pass to the colon where they penetrate the mucosa forming a submucosal or mural nodule. In primary infections, mural lesions are small and heal after the 4th stage larvae exit into the lumen. However, when a host is reinfected, larvae may become trapped in the nodule by immune-mediated inflammation. Clinical signs range from none to severe diarrhea, weight loss, anemia, hypoproteinemia and mortality. Grossly, white, yellow, red, or black 2–5 mm nodules stud the colonic serosa and mesentery. Viable larvae may be seen in some nodules. Inflammation varies from necrotizing and hemorrhagic to granulomatous and can become suppurative due to secondary bacterial invasion (Fig. 15.32). The overlying mucosa may be normal, thickened, covered by a diphtheritic membrane or contains small ulcers. Rupture of the nodules or transmural extension of inflammation is associated with peritonitis and mesenteric/omental adhesions. If

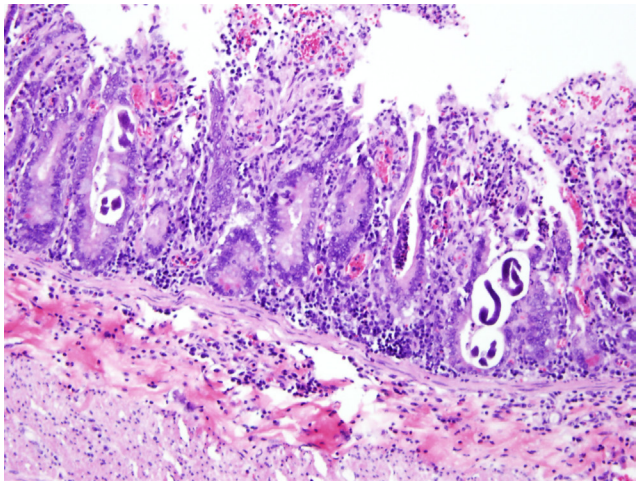

FIGURE 15.31 ***Strongyloides stercoralis*** **colitis in a chimpanzee.** Parasites within colonic crypts are associated with inflammation and necrosis.

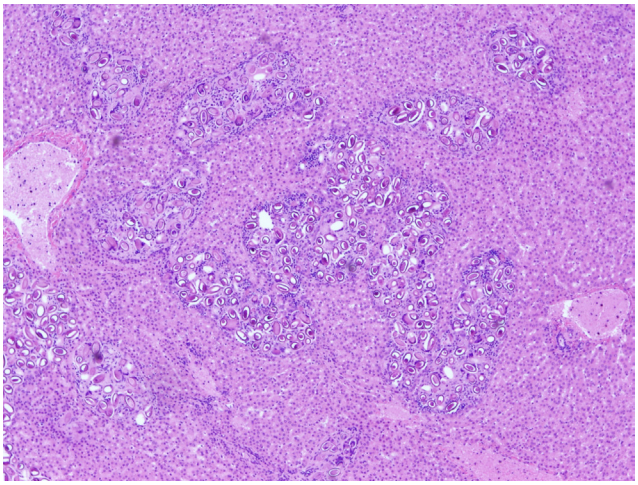

FIGURE 15.33 **Hepatic capillariasis in a mountain gorilla.** Severe granulomatous inflammation surrounds nematode eggs laid in serpiginous tracts created by female worms.

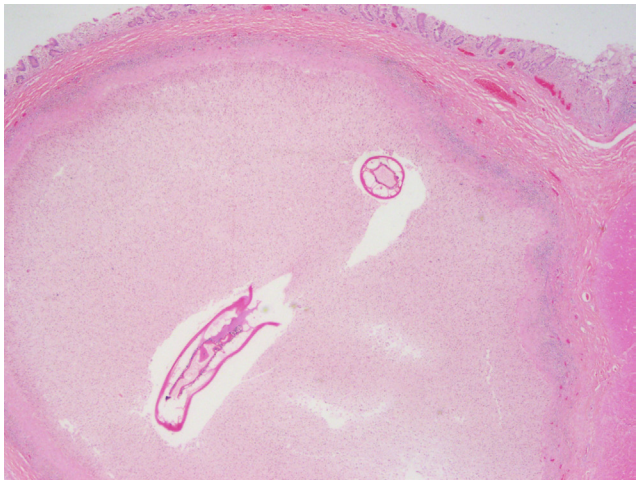

FIGURE 15.32 **Colonic oesophagostomiasis in a mountain gorilla.** A large, demarcated, mural nodule composed of chronic granulomatous and suppurative inflammation contains sections of intralesional spirurid nematodes.

hypoproteinemia is present, hydropericardium and hydrothorax can occur. Ante mortem differentiation of the ova and larvae of hookworms and nodular worms in fecal samples is not always possible and PCR techniques have been developed for more reliable diagnosis (Verweij et al., 2007).

Capillariasis due to ***Calodium hepatica*** **(syn.** ***Capillaria hepaticum*****)** is found worldwide. Many species, including nonhuman primates, can be infected; rodents are the natural host. Infection occurs via ingestion of eggs from environments contaminated with decomposed liver tissue or the feces of a predator or scavenger that has eaten an infected animal. Infection is identified at necropsy, and in mountain gorillas is usually incidental but occasionally severe in infants (Graczyk et al., 1999). Eggs with thick walls and bipolar caps (opercula) and adults with aphasmid morphology (hologonic, stichosome, bacillary bands, and characteristic eggs) are found in tracks in the liver parenchyma, often near portal areas. Reaction to the parasites varies from none to marked granulomatous hepatitis (Fig. 15.33). ***Capillaria brochieri*****,** an enteric parasite, is reported to cause fatal diarrhea in bonobos (Justine 1988).

Mammomonogamous laryngeus is a syngamid nematode with a broad host range that is related to the gapeworms of birds and is endemic to Southeast Asia, the Caribbean and Brazil. Infections accompanied by respiratory signs and death are documented in a semi-wild population of Sumatran orangutans in Indonesia (Foitová et al., 2008). The life cycle is unknown, but is likely direct with fecal–oral transmission. Eggs and occasionally whole nematodes are coughed up, swallowed and shed in feces. Grossly, large numbers of parasites occur in upper and lower airways of young orangutans dying with dyspnea and lethargy. Microscopic lesions are not described in orangutans, but in affected bovids, mucosal edema and polyoid proliferations are found at nematode attachment sites. Eggs of *Mammomonogamous* sp. are also identified in feces of western lowland gorillas in the Central African Republic, but lesions are not yet described (Cervená et al., 2017).

Larval migrans, due to ***Baylisascaris sp.*** and ***Angiostrongylus sp.*****,** can be a problem in zoo-housed gibbons and orangutans (Emerson et al., 2013; Hanley et al., 2006; Miller et al., 2006). Definitive hosts of *Baylisascaris* spp. include raccoons (*B. procyonis*) and skunks (*B. columnaris*). The infection is found throughout the US. Parasite migration tracts in the brain are grossly malacic with or without hemorrhage. Necrosis, spongiosis, and nonsuppurative inflammation are present histologically. The larval nematodes, with characteristic prominent lateral alae, can be surprisingly hard to find in brain sections. Systemic vascular involvement is not a feature.

Parastrongylus (Angiostrongylus) cantonensis and ***P. costaricensis*****,** parasites of rats with a snail intermediate host that have been introduced and become endemic in the southeastern United States, can cause larval migrans in

zoo-housed gibbons, orangutan, owl monkeys, and callitrichids and in native wildlife including raccoons and opossums. ***P. cantonensis*** generally causes pulmonary angiostrongyliasis or eosinophilic meningingoencephalitis and/or myelitis. ***P. costaricensis*** causes abdominal angiostrongyliasis. Inflammation is usually eosinophilic and necrotizing or granulomatous and the nematodes are usually visible in vessels of lung or lumen of heart (*P. cantonensis*) or in mesenteric vessels (*P. costaricensis*).

Apes are host to a variety of **cestodes (tapeworms),** some of which, especially larval forms, are highly pathogenic. Of greatest concern is **hydatid disease** due to ***Echinococcus granulosa*** (dog definitive host) or ***E. multilocularis*** (fox definitive host). Individuals with the former parasite may be infected in countries of origin, but those with the latter are infected after importation as *E. multilocularis* only occurs naturally in the Northern Hemisphere. Mortality from hydatid disease is reported in gorillas in zoos in the US, Europe, and Japan (Benirschke and Adams, 1980; Rehmann et al., 2003; SSP data base). Gross lesions consist of abdominal enlargement due to uni- or multiloculated cysts that contain many daughter brood capsules and daughter cysts. Rupture of the cyst(s) leads to seeding of the peritoneum by the asexually dividing larvae, causing florid, chronic, effusive peritonitis. The liver may be replaced by necrosis and cystic, caseous or fibrotic nodules. Renal involvement may occur. Histologically, the wall of hydatid cysts, due to *E granulosa,* has a characteristic hyaline, laminated appearance. Inflammation ranges from suppurative to granulomatous. Hydatid disease differs from **cysticercosis** in that the cysticercus is a single thin walled cyst with single invaginated larval scolex in CNS or viscera (Sagartz and Tingpalapong, 1974). An unusual, fatal case of larval cestodiasis due to ***Versteria sp.*** (mustelid carnivore definitive host) occurred in a juvenile orangutan with a short clinical course of lethargy, anorexia and cough and gross lesions of hepatosplenomegaly, pulmonary hemorrhage and pericardial and thoracic effusions (Goldberg et al., 2014). On histology the liver contained uni- and multilocular, unencapsulated, thin walled cysts containing marginated, multinucleated parasitic protoplasm. Similar cysts were present in the lungs and spleen, often in blood vessels.

Intestinal tapeworms of the genera ***Bertiella*** and ***Anoplocephla*** are commonly seen in apes (Doležalová et al., 2015; Nurcahyo et al., 2017). Wild mountain gorillas, especially older adults, are often heavily parasitized by ***A. gorillae*** (Sleeman et al., 2000). These animals are often in poor condition, but whether the tapeworms are opportunistic or pathogenic is unclear.

Protozoa

The most important protozoan disease of captive apes is **balantidiasis** due to ***Balantidium coli***. Amoebic infections are also common and vary from incidental enteric colonization (e.g., ***Entamoeba dispar***) to disseminated fatal disease (e.g., ***Balamuthiua mandrillaris***). ***Plasmodium spp.*** infections are common in free-living western gorillas, chimpanzees, orangutans and gibbons, but clinical malaria is infrequently documented. Other protozoan infections, such as **cryptosporidiosis, cyclosporidiosis and giardiasis** have been detected by microscopic and molecular fecal examinations, but rarely associated with clinical disease (e.g., Sak et al., 2014; Mynářová et al., 2016).

Balantidium coli is a ciliated protozoan with worldwide distribution and broad host range including apes, other nonhuman primates, and humans (Nakauchi, 1999). Molecular studies have resulted in the suggested reassignment of the primate parasites to the genus ***Neobalantidium*** (Pomajbíková et al., 2013). *B. coli*-like ciliates are identified in free-ranging, sanctuary, zoo and colony housed apes, though infection is much more common in captive than in free-ranging populations (Kilbourn et al., 2003; Pomajbíková et al., 2010a). *Balatidium* is generally considered commensal, but can become invasive when animals are immune compromised, stressed or suffering from other causes of diarrhea (e.g., salmonellosis). Morbidity and mortality are described in western lowland gorillas, chimpanzees, and orangutans in zoos and in semi-captive (rehabilitant) orangutans (Lankester et al., 2008). Captive diets high in starch may allow for overgrowth of the organisms (Schovancová et al., 2013). The most common gross lesion is ulcerative typhlocolitis with hyperemia and hemorrhage in the colon and cecum and hemorrhagic diarrhea (dysentery) (Lankester et al., 2008). Histologically, the protozoa are present in the lumen, on the mucosal surface, within ulcer beds and throughout the wall (Fig. 15.34). The trophozoite stage has two nuclei and the cyst stage has a

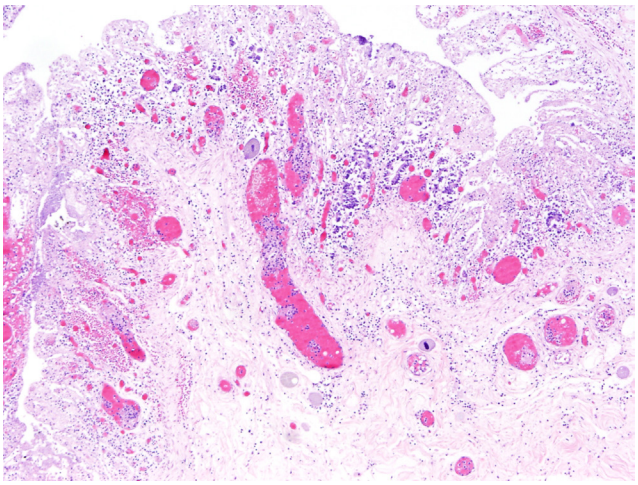

FIGURE 15.34 Invasive balantidiasis with hemorrhagic typhlocolitis in a western lowland gorilla. Round to ovoid amoeboid, amphophilic protozoa with a prominent curved macronucleus are present in the mucosa and submucosa. Infection and inflammation are associated with multifocal necrosis and hemorrhage.

large, curved or horseshoe-shaped macronucleus. These and the distribution of circumferential cilia (holotrich) are useful morphologic features that aid in differentiating them from commensal ciliated protozoans, such as ***Troglodytella gorillae*** and ***T. gabonensis*** in wild gorillas and ***T. abraesarti*** in chimpanzees, bonobos, gorillas, and siamangs in captivity (Pomajbíková et al., 2010b).

Cerebral and systemic amoebiasis due to ***Balamuthia mandrillaris***, a free-living, soil dwelling, leptomyxid amoeba with global distribution, is a serious emerging infection of gorillas, and, less frequently, other apes (orangutans, gibbon), monkeys, and humans (Canfield et al., 1997; Gjeltema et al., 2016; Rideout et al., 1997). It accounts for almost 3% of gorilla deaths in the North American SSP population and is described in zoo-housed apes in Europe and Australia. The presumed route of infection is inhalation of airborne cysts from contaminated soils or, rarely, through skin wounds. Brain lesions may be visible grossly as foci of malacia, congestion, or hemorrhage in both gray and white matter without specific geographic distribution (Fig. 15.35). Histologically, the infection is both necrotizing and granulomatous and often vasocentric with associated fibrinoid vasculitis (Fig. 15.36A, B). Organisms often cluster in Virchow-Robin spaces, but immunological staining reveals wider distribution. In some cases granulomatous inflammation and fibrosis, which cause mass lesions suggestive of neoplasia, are present in liver, kidney, pancreas and lymph nodes. Differential diagnosis includes cerebral amoebiasis due to *E. histolytica* or other free living amoeba (e.g., *Nigleria* or *Acanthamoeba* spp.). Amoeba are identified on the basis of nuclear morphology and shape and size of the karyosome. *E. histolytica* has a distinctive large karyosome. *Balamuthia* and *Acanthamoeba* are sometimes difficult to differentiate, though *Balamuthia* sometimes has a double endosome (Fig. 15.36B). Immunohistochemistry and PCR differentiation is available through the United States Centers for Disease Control (CDC) and some diagnostic laboratories (e.g., California Animal Health Laboratory System).

Intestinal amoeba are fairly commonly detected on routine fecal examinations of both managed and free-living apes (Jirků-Pomajbíková et al., 2016; Kuze et al., 2010) Amoeba identified include ***Entamoeba dispar*** and ***E. histolytica***, ***Entamoeba*** **spp.,** ***Dientamoeba*** fragilis and other **Dientamoeba spp., and Iodoamoeba sp..** Although ***E. histolytica*** is considered to be the most pathogenic of the enteric amoeba it is less often detected in apes than in OW monkeys. Lesions of *E. histolytica* include ulcerative colitis with "flask shaped ulcers" expanding into the submucosa and amoebic hepatic and cerebral abscesses. ***Dientamoeba***

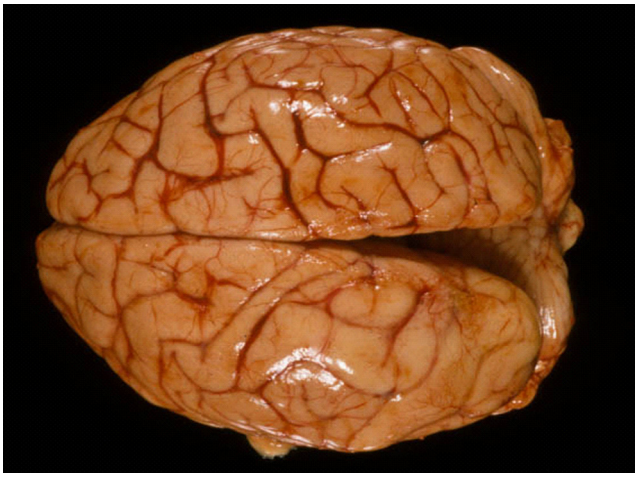

FIGURE 15.35 Amoebic encephalitis due to *Balamuthia mandrillaris* in an orangutan. A focal area in which the parenchyma appears roughened and the vasculature is indistinct is present in the left occipital lobe near the longitudinal fissure.

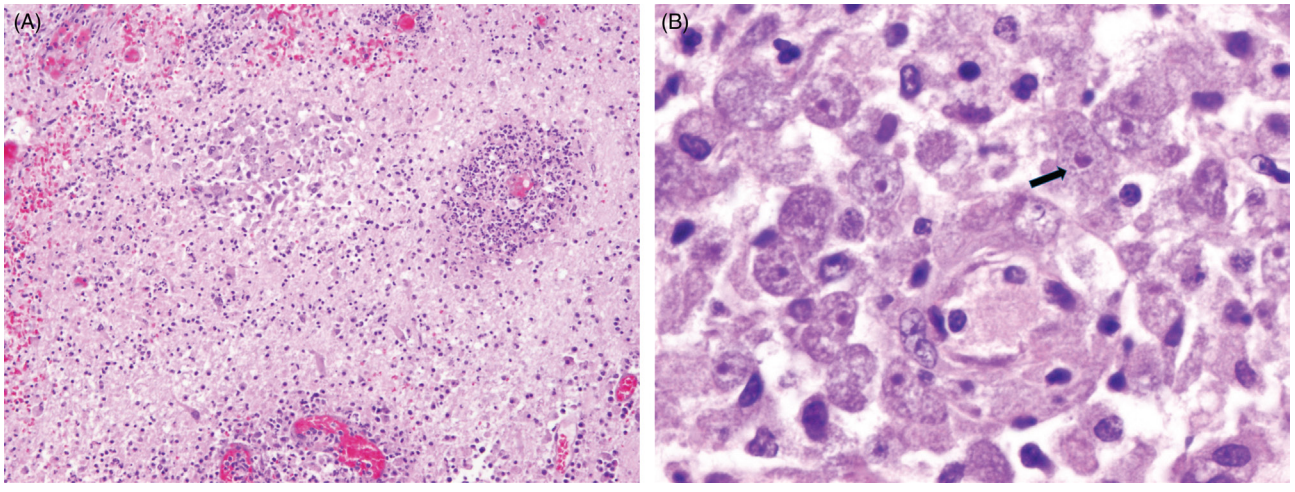

FIGURE 15.36 Amoebic encephalitis due to *Balamuthia mandrillaris* in an orangutan. (A) Infection causes regionally extensive malacia and necrotizing vasculitis (B) Numerous amoeboid protozoa form a thick perivascular cuff. A characteristic double endosome is present in one amoeba *(arrow)*.

fragilis is recognized as an emerging human pathogen causing chronic irritable bowel-like symptoms and may also be pathogenic in gorillas (Lankester et al., 2010). Signs include persistent diarrhea, without blood, and weight loss that resolves with appropriate treatment, such as metronidazole.

American trypanosomiasis or **Chaga's disease**, caused by ***Trypanosoma cruzi***, occurs in captive nonhuman primates, including gibbons and chimpanzees, housed outdoors in endemic areas of the southern Unites States and Central and South America (Bommineni et al., 2009; Seibold and Wolf, 1970). Transmission is percutaneous via feces from the triatomid or "kissing bug" vector contaminating the bite wound, or through ingestion of infected bugs. Transplacental transmission and congenital infection is described in marmosets and baboons, but not in apes. Heart failure is the most common presentation in all primates. Megaesophagus, common in humans, is not described in nonhuman primates. Gross lesions include cardiomyopathy, myocardial necrosis or fibrosis, pulmonary edema, and effusions. Histologically there is primarily mononuclear myocarditis and myocardial necrosis. The amastigote forms of *T. cruzi* are seen in pseudocysts in heart, skeletal muscle, and reticuloendothelial cells. They are distinguished from other protozoans that might infect the myocardium (e.g., *Toxoplasma* sp.) by the presence of both nucleus and bar-shaped kinetoplast. Trypomastigotes or trypanosomes are rarely seen in blood smears from infected chimpanzees.

Malaria due to ***Plasmodium* spp.** is one of the globally most important diseases of humans, causing both lifelong morbidity and mortality in tropical and subtropical areas of the world. Nonhuman primates are naturally infected with malarial parasites often identical or closely related to human pathogens. Cross-species, mosquito-mediated transmission is well documented (Makanga et al., 2016; Ngoubangoye et al., 2016). Identified species include: *P. rodhaini* in chimps and western gorillas (similar to *P. malariae,* zoonotic); *P. reichenowi* in chimps and western gorillas (ancestor of *P. falciparum;* not zoonotic); *P. schwetzi* in chimps and western gorillas (similar to *P. vivax;* zoonotic); *P. pitheci*, *P. sylvaticum, P. inui, P. cynomolgi*, and human *P. vivax* in orangutans; and *P. hylobati*, *P eylesi, P. youngei,* and *P. jeofferyi* in gibbons (Boundenga et al., 2015; Eyles et al., 1964; Reid et al., 2006).

Plasmodia require an arthropod vector, usually an anopheline mosquito. Infection in apes is generally subclinical, but in gibbons may be associated with mild cyclic depression due to anemia. In confiscated orangutans "malaria-like symptoms" have been abrogated by antimalarial treatment. Repeated thick blood smears examined by experienced lab personnel are necessary for diagnosis, and speciation can sometimes be made on morphology alone. PCR is available for differentiation of related species. Blood smears reveal intraerythrocytic gametes and, in some species, schizonts. Gross pathology, based on experimental studies, includes hepatosplenomegaly (especially if the plasmodium species has extraerythrocytic schizogony). Hepatic and splenic extramedullary hematopoiesis, Kupffer cell hyperplasia, and expansion of the mononuclear phagocytic system cells in the spleen are associated with black granular pigment (hemazoin) in phagocytic cells. Hemazoin is refractile, birefringent, and does not stain with iron stains (e.g., Perl's). It must be differentiated from acid hematin, a fixation artifact. Cerebral malaria, a severe consequence of human malaria due to sludging of parasitized red cells in brain capillaries, is reported in simian primates but not apes.

Ectoparasites and Mites

Mange due to ***Sarcoptes scabei* (scabies)**, is reported in free-living gorillas and chimpanzees and can cause death in infants (Graczyk et al., 2001; Williams et al., 2008). Skin lesions include alopecia associated with florid hyperkeratosis and occasionally nodule formation. Histologically, mites are visible in deep epidermal tunnels. Morbidity and mortality are associated with alopecia, anorexia, and weight loss. The source of the mites may be humans or other animals. ***Pangorillalges gorilla*** is a common, gorilla-specific mite that can also causes mange in mountain gorillas (Nutter et al., 2005b). It is a much less serious infection than scabies, although alopecia and pruritis may be present. ***Psorergates mange*** in siamang causes pruritis, scaley skin, and multifocal alopecia (Atkins et al., 2008). Histologically mites are present just beneath or within the stratum corneum. Whole mites are needed for speciation or mite specific DNA can be amplified from host feces.

Demodex-like mites are seen incidentally in sebaceous glands of mountain and western lowland gorillas and are likely present in all apes. Though small sebaceous glands are associated with hair follicles over the entire body, very large sebaceous glands are present only on the brow ridge, cheeks, lips and genital area. Ducts of these complex sebaceous glands provide habitat for *Demodex* mites. Eccrine sweat glands, found over the entire body in gorillas and chimps (except lips, nose, male prepuce and female labia), and apocrine sweat glands (associated with some hair follicles and scent glands, such as the sternal scent glands of gibbons and orangutans and the axillary organ of African apes) are not affected (Stoddart. 1998).

Respiratory mites are found in the nasal cavity, sinuses, larynx, trachea or lungs. ***Pneumonyssus oudemansi*** is described in chimps and gorillas and ***Rhinophagia pongicola*** in the frontal sinus of orangutans (Fain, 1957, 1958). In zoo-housed gorillas and bonobos, respiratory mites are occasionally seen during tracheal intubation or on nasal secretions cytology.

Pediculosis (lice infestation) in free-living chimpanzees and gorillas can be especially severe in young or debilitated

animals. ***Pthirus gorilla,*** a blood sucking louse related to the human pubic louse, is found all over the body in gorillas (Reed et al., 2007). Nits (eggs) and adults are readily visible grossly. Chimpanzees can be heavily infested with the blood-sucking louse, ***Pediculus schaeffi,*** which is related to the human head louse (Herd et al., 2015).

E-SLIDES

15.e1 **Fibrosing cardiomyopathy, athero- and arteriosclerosis, lowland gorilla, heart.** In this adult gorilla non-occlusive atherosclerosis in epicaridal and intramuscular coronary arteries and intramuscular arterio and arteriolosclerosis with medial hypertrophy and hyalinzation are associated with dissecting fibrosis, myofiber hypertrophy (distorted and enlarged nuclei) mild lipofuscinosis and atrophy of entrapped fibers. (see Figs. 15.3, 15.4 and 15.9). eSlide: VM05269

15.e2 **Fibrosing cardiomyopathy, myocardial necrosis, and arteriosclerosis, lowland gorilla, heart (septum).** In this section, from an animal dying after long-term treatment for chronic heart disease, dissecting myocardial fibrosis is associated with myofiber hypertrophy (characterized by karyomegaly and nuclear distortion), multifocal acute myofiber necrosis with mixed inflammation and myophagia and arteriolosclerosis of intramuscular arterioles. (see Figs. 15.3 and 15.4). eSlide: VM05270

15.e3 **Oral epithelial hyperplasia, adult common chimpanzee, oral mucosa.** Oral epithelial hyperplasia, also called oral papillomatosis in common chimpanzees and bonobos is a self-limiting process that may become recrudescent. There is acanthosis with hyperplasia of the basal layer and deep often anastomosing epithelial pegs. Intranuclear inclusion bodies due to the causative papillomavirus(es), as is the case in this slide, are not always seen. (see Figs. 15.18 and 15.19). eSlide: VM05271

15.e4 **Strongyloidiasis, Strongyloides stercoralis, common chimpanzee, small intestine and colon.** Mature strongloides females and eggs are present in the inflamed duodenum while larvae are present more distally and have invaded the mucosa colonic mucosa causing colitis, indicating potential hyperinfection with this reverse zoonosis. (see Fig. 15.31). eSlide: VM05272

15.e5 **Esophagostomiasis (nodular worm, Oesophagostomum stephanostomum), mountain gorilla, colon.** Mural abscesses surround profiles of a strongyle nematode. There is mild multifocal inflammation in the mucosa and necrosis of scattered crypts. Also included on the slide are sections of normal ovary, duodenum and jejunum. (see Fig. 15.32). eSlide: VM05286

15.e6 **Amoebic encephalitis, Balamuthia mandrillaris, Bornean x Sumatran orangutan, brain occipital lobe.** Amoeba are present individually and in clusters in this region of severe necrotizing encephalitis. They can be distinguished from host macrophages by nuclear morphology and grey staining cytoplasm. (see Fig. 15.36). eSlide: VM05294

E-ONLY CONTENTS

INTRODUCTION TO APES

The Gibbons (family *Hylobatidae*)

Gibbons, the "lesser" or "small" apes, are catarrhine primates indigenous to Southeast Asia. They are thought to be an evolutionarily intermediate between Old World (OW) monkeys and the great apes. There are currently four recognized genera: *Nomascus*, *Hylobates*, *Hoolock,* and *Symphalangus* and 16 species. The first two are polyspecific, while *Hoolock* and *Symphalangus* are monospecific. Of note are the large scale karyotypic rearrangements that have occurred among the gibbon genera with diploid numbers of 38 (*Hoolock*), 44 (*Nomascus*), 50 (*Symphalangus*), and 52 (*Hylobates*) (Chaterjee, 2009), though hybridization has occurred between *Nomascus* and *Hylobates* and *Hylobates* and *Symphanangus* (Baichaeron et al., 2014; Myers and Shafer, 1979). All species are endangered or critically endangered (IUCN Red List). The full genome of a northern white-cheeked gibbon has been sequenced. It is thought that the gibbon lineage experienced rapid expansion or radiation about 5 million years ago, possibly due to dramatic climatic and habitat changes in the region (Carbone et al., 2014). In contrast to the great apes, gibbons exhibit little sexual size dimorphism though coat color dimorphism is found in several species. Most studies in wild gibbons have been directed toward behavioral ecology with little information on disease and health issues of wild populations, and although gibbons are common in zoos and have been used as research animals, there is surprisingly little in the literature on their spontaneous diseases and pathology.

The Great Apes

The great apes, also called hominid primates, include: the bonobos (*Pan paniscus*), (common) chimpanzees (*Pan troglodytes*), and gorillas (*Gorilla* sp.) of Africa and the orangutans (*Pongo* sp.) of Southeast Asia. There is one species of bonobo, which diverged from the common chimpanzees about 0.8–1.7 million years ago (Yu et al., 2003). The bonobo genome has been sequenced and compared with that of chimpanzees and humans (Prüfer et al., 2012). Bonobos are endemic to the Democratic Republic of Congo (DRC) and are held in zoos in Europe, the Americas and Asia, as well as in sanctuaries in DRC, but are fewer in number and much less well studied than common chimpanzees.

There are four currently recognized subspecies of common chimpanzees: the Central African chimpanzee (*Pan troglodytes troglodytes)*, the Eastern chimpanzee (*P. t. sweinfurthii)*, the Western or savannah chimpanzee (*P. t. versus*) and the Nigeria-Cameroon chimpanzee (*P. t. vellerosus [eliott]*). Many zoo and laboratory-housed chimps are hybrids of sub-species (Ely et al., 2005). The Association of Zoos and Aquariums (AZA) Chimpanzee Species Survival Program (SSP) manages chimpanzees as one species. While many of the chimpanzees in European zoos are also hybrids, the European AZA's (EAZA) European Endangered Species Program (EEP) manages Western chimpanzees in a separate studbook (Hvilsom et al., 2013). There is evidence that there are behavioral or "cultural" differences between the subspecies (Lycett et al., 2011) that have a genetic basis. There is also variation in genes coding for bitter taste receptors, possibly reflecting selection based on different diets in geographic ranges of the different subspecies (Hayakawa et al., 2012). Chimpanzee viruses have also been affected by the divergence of subspecies a million years ago (Hey, 2010). For example, SIVcpzPtt in the Central African chimpanzee is the progenitor of HIV-1, while the SIVcpzPts of Eastern chimpanzees does not seem to cross into humans. Thus far no SIVs have been found in bonobos in the wild or in managed care (Li et al., 2012).

The chimpanzee genome, was initially reported in 2005 (Chimpanzee Genome Sequencing Consortium) and whole genome comparisons between humans and chimps have provided insight into several human diseases. Comparisons of chromosome morphology and sequence function is an avenue of comparative research (Gross et al., 2006). Homologues of syndromes, such as Downs and XXX have been identified. In terms of health issues and pathology, the common chimpanzees are the best studied of the apes, largely due to maintenance of large laboratory colonies.

There are currently two species of gorilla, each with two subspecies: the Western gorillas (*Gorilla gorilla*) with subspecies Western lowland gorilla (*G. g. gorilla*) and Cross-river gorilla (*G. g. dehlei*), and the Eastern gorillas (*Gorilla beringei*) with two subspecies the mountain gorilla (*G. b. beringei*) and the Eastern lowland or Grauer's gorilla (*G. b. graueri*). Both Western lowland gorilla and Eastern gorilla genomes have been sequenced (Scally et al., 2012; Xue et al., 2015). Mitochondrial DNA of the Western lowland gorilla has also been sequenced (Hu et al., 2016). All gorillas currently in AZA zoos are Western lowland gorillas; European zoos hold mainly Western lowland gorillas, although there is currently one elderly Eastern lowland gorilla in one zoo. There are no mountain gorillas in zoos. In Africa, orphaned Eastern lowland gorillas and mountain gorillas are cared for in two separate sanctuaries, with the ultimate aim of reintroduction into the wild (http://gracegorillas.org/; https://virunga.org/projects/gorilla-orphans/). Orphaned and confiscated Western lowland gorillas are also in sanctuaries in range countries (http://www.pasaprimates.org/).

The orangutans consist of three species: the Bornean orangutan (*Pongo pygmaeus*) of which the IUCN (International Union for the Conservation of Endangered Species) recognizes three subspecies (*P. p. morio*—Northeast Bornean Orangutan, *P. p. wurmbii*—Central Bornean Orangutan and *P. p. pygmaeus*—Northwest Bornean Orangutan)

and the Sumatran orangutans (*Pongo abelii*) and the newly recognized Tapanuli orangutan (*Pongo tapanuliensis*) (Nater et al., 2017). Bornean orangutans are listed as endangered, while Sumatran orangutans and Tapanuli are critically endangered (IUCN Red List http://www.iucnredlist.org/). The genomes of Bornean, Sumatran and Tapanuli orangutans have been sequenced (Locke et al., 2011; Nater et al., 2017). In the past, orangutans were managed in zoos as a single species, and there are many Sumatran × Bornean hybrids. The International Orangutan Studbook includes the two species as well as hybrids, but both AZA and EAZA manage the two species separately, and have a moratorium on breeding the hybrids. Orangutans are often called "the neglected ape" because of the relative paucity of scientific and health studies, compared to the African apes.

The Natural History of Apes

Gibbons in the wild are largely arboreal, moving about the tropical forests swinging hand over hand (brachiating). When they move on the ground they walk bipedially often raising their arms above the head for balance. Anatomic adaptions to facilitate this life style include very long arms and forearms, hands with very long fingers and elongated thumbs, and short legs with prehensile feet. Diet in the wild consists mainly of fruit with varying amounts of leaves and insects (Whitten, 1982). The siamang is considered to be primarily follivorous (Leigh, 1994). An interesting aspect of gibbon natural history is their vocalization with duetting between mates (Clarke et al., 2006; Tenaza 1976). Calling is facilitated by throat sacs, most prominent in the siamang in which the there is a balloon like expansion during vocalization.

Orangutans are largely arboreal forest dwelling animals, and females and juveniles often use saplings to catapult across small clearings to avoid descending to the ground. Orangutans in zoos often spend considerable time on the ground, while wild Bornean orangutans spend less than 5% of the time on the ground (Ashbury et al., 2015). Females and juveniles mainly come down to eat termites, while the adult males become terrestrial mainly in traveling distances across clearings; all age classes come down to drink and "bathe" in standing water. However, depending on habitat, anthropogenic disturbances do not drive terrestriality (Ancrenaz et al., 2014). Diet is strongly frugivorous, though fallback foods, such as flowers, leaves, bark, insects, and vertebrates including fish and, rarely, smaller mammals, such as slow lorises and squirrels, are also eaten depending on the season and the availability of fruit (Buckley et al., 2015; Hardus et al, 2012; Russon et al., 2014). Protein is often limited in orangutan diets (Vogel et al., 2012). Orangutan metabolism has evolved to deal with the feast or famine situation of periodic fruit abundance (masting) and failure (Harrison et al., 2010; Kanamori et al., 2017), which may account for some of the metabolic problems encountered in captive management situations (reviewed in Lowenstine et al., 2016). Geophagy (eating earth) has been reported in orangutans (Mahaney et al., 2016).

The African apes are all generally forest animals though habitats consisting of mosaics of woodlands and savannahs are use by both bonobos and common chimpanzees. Chimpanzees, bonobos, and gorillas all spend more time on the ground than do the Asian apes, utilizing trees as sleeping sites and for travel. Adaptations for this life style include knuckle walking with the dorsal surface of phalanges 2 and 3 of digits 2–5 contacting the ground, necessitating specialize knuckle pads on the fingers, and a flatter backed posture in apes than monkeys. Both *Pan* species are considered "highly frugivorous omnivores" meaning that fruits, in addition to other plant parts, are major components of their diets. Gorillas are more strictly vegetarians, eating a wide variety of plant types and parts including grasses, leaves, stems/pith, bark, fruits and, occasionally, insects (Deblauwe and Janssens, 2008). Western lowland gorillas are more strongly frugivorous than the Eastern gorillas; however, when Western gorillas and chimpanzees utilize the same forests, there is partitioning of resources such that chimpanzees are more frugivorous and gorillas rely more on herbaceous plants (Oelze et al, 2014). Insectivory is well described in the African apes (Rothman et al., 2014) and consists primarily of consumption of termites and ants (Hamad et al., 2014). Both bonobos and chimpanzees kill vertebrate prey including rodents and smaller nonhuman primates, and although providing a good source of high quality protein, this is a minor part of their diets (Moore et al., 2017; Sakamaki et al 2016; Tennie et al., 2014). African apes obtain minerals through geophagy, which may also serve as a way to ameliorate digestive problems including parasitism, though soil ingestion may conversely pose a risk for parasite acquisition (Krishnamani and Mahney, 2000). Rotten logs may be eaten as a source of sodium (Rothman et al., 2006).

Conservation Status

All the apes are listed as endangered or critically endangered (see Supplemental Materials Table e1) and international transfer of diagnostic samples from wild apes requires CITES exit and entry permits. In Asia, threats to wild populations of gibbons include anthropogenic factors, such as direct predation, exploitation for pet trade, deforestation, and nonanthropogenic factors including climate change and clouded leopard predation (Dooley and Judge, 2015; Morino, 2010). Hybridization in captive settings threatens some subspecies. Anthropogenic threats to orangutan populations include deforestation by logging and palm oil plantations, habitat fragmentation, wildfires (often related to human activities), and hunting for the pet trade and bush meat. Other than humans, orangutans have no natural predators. For the African apes, threats are similar: habitat disruption and loss due to mining and logging, hunting for commercial bush meat trade, accidental

entrapment (snares set for other animals), and also include diseases, such as Ebola (Western lowland gorillas and chimpanzees), anthrax-like infection (mainly chimpanzees) and respiratory diseases (chimpanzees, mountain gorillas) (Walsh et al., 2003). Leopard predation may be important in some populations (chimpanzee, bonobo, western lowland gorillas) (d'Amour, 2006).

ADDITIONAL UNIQUE FEATURES

External Anatomy

The skin of gorillas and chimpanzees has been described in detail (Ellis and Montagna, 1962, Montagna and Yun, 1963). Small sebaceous glands associated with hair follicles are located over the entire body with very large sebaceous glands on the brow ridge, cheeks, lips, and genital area. These sebaceous glands provide a natural habitat for Demodex mites. Eccrine sweat glands are found over the entire body in gorillas and chimps with the exception of lips, nose, male prepuce, and female labia. Apocrine sweat glands are associated with some, but not all, hair follicles and are abundant in the axillae where they and eccrine glands combine to form the axillary organ, the main scent gland in African apes (Stoddart, 1998). Sternal scent glands, consisting of highly coiled apocrine glands, have been described in gibbons and orangutans.

"Fingerprints" (dermatoglyphs) are present on the digits of all apes and on the knuckle pads of gorillas and chimpanzees (Montagna, 1972). The knuckle pads consist of thickened dermis and epidermis on the hands to accommodate knuckle walking.

Ischial callosities, grossly, and histologically similar to those in OW monkeys, are found in all gibbons. Less than half of chimpanzees also have callosities, but they are not attached to the underlying ischial tuberosities and are less heavily keratinized than those of OW monkeys and gibbons. Callosities are rare in orangutans and gorillas (Vilensky, 1978).

Perineal sexual swelling (tumescence) is present and florid in the glabrous skin of the perineum in chimpanzees and bonobos during the follicular (estrogenic) phase of the estrous cycle (Dahl, 1988; Paoli et al., 2006). Swelling also occurs during the first trimester of pregnancy. Perineal sex skin histology is similar histologically to that of the OW monkeys. Sexual swelling is subtle in gibbons and orangutans (Nunn, 1999). Labial swelling occurs in orangutans during pregnancy (Sodaro, 1988). Transient labial intumescence occurs without perineal swelling in gorillas (Nadler, 1975).

Skeletal Anatomy

Cranial sutures are unfused at birth to facilitate passage of the relatively large head of the infant through birth canal and to allow for brain growth postnatally. They close earlier in the apes than in humans (Balolia 2015; Cray et al., 2010, 2010, 2011, 2012). The anterior fontanelle closes around the time of birth in most hominids and by 3 months in chimpanzees (12–18 months in human infants). Finding open anterior or posterior fontanelles in neonatal apes, other than chimpanzees, is suggestive of prematurity (https://carta.anthropogeny.org/moca/topics/age-fontanelles-cranial-sutures-closure).

Pneumatic spaces of the hominid skull include ethmoid, sphenoid, frontal, and maxillary sinuses, of which the maxillary sinuses are generally the largest (Koppe et al, 1995, 1996; Pruschoft et al., 2002; Rae and Koppe, 2000). In gibbons frontal sinuses may be lacking. This is in contrast to NW and OW monkeys in which, if there are pneumatized spaces, only the maxillary sinus is present. The use of magnetic resonance images (MRI) and computed tomography (CT)scans has enhanced our understanding of the three dimensional anatomy of the sinuses and their role in respiratory disease. The maxillary sinus surrounds the roots of the "cheek teeth" in gibbons, chimpanzees, and gorillas, but not in orangutans, and dental disease in captive apes may cause sinusitis. Sinusitis has been reported in all the apes and is thought to contribute to the development of air sac infections in orangutans (Steinmetz and Zimmermann, 2011).

All apes have seven cervical vertebrae. The cervical vertebrae are short and the atlanto-occipital joint space very narrow (Manfreda et al., 2006). As a consequence, the atlas is often left with the skull when the head is disarticulated during necropsy.

The postcervical vertebral segment numbers vary even within species (Schön and Straus, 1969; Williams, 2012, Williams and Russo, 2015). Gibbons have 13 thoracic vertebrae, 4 or 5 lumbar, 4 or 5 sacral and coccygeal vertebrae. Chimpanzees and gorillas have 13 thoracic, 3 or 4 lumbar and 5 or 6 sacral, while orangutans have 12 thoracic, 4 lumbar, and 4–6 sacral vertebrae. All apes are tailless and coccygeal vertebrae are generally entirely within the contours of the rump. There are, on average, 4 coccygeal vertebrae in chimpanzees and gorillas and 3–7 in gibbons.

Rather than the elongate individualized "sternabrae" of the New and Old World monkeys, the sternum of great apes consists of a shield-shaped manubrium, flattened body or mesosternum and a small xyphoid. The manubrium and the xyphoid are articulated. The clavicle is well developed in all apes (Voisin 2006). Sternoclavicular arthritis has been seen in the apes and this joint should be examined at necropsy.

It is generally thought that orangutans do not have a round ligament of the head of the femur, which, along with a relatively shallow acetabulum, may enable rotational flexibility. However, personal and published observations of other specimens detected a fovea capitus and round ligament, suggesting that absence may be either recently derived or pathological (Crelin 1968; Lowenstine et al., 2016). To

resolve this controversy, pathologists need to carefully examine the coxofemoral joints of orangutans at necropsy and document presence or absence of the ligament.

There is much variation in the fusion time of the growth plates of the long bones of the appendicular skeleton such that it is difficult to make generalizations in terms of expected age at fusion. Please consult primatology references, such as Bolter and Zihlman (2012) and Winkler (1996).

Regional Anatomy of the Oral Cavity and Neck

The dental formula for all the apes, like OW monkeys, is: I 2/2, C 1/1, P 2/2, M 3/3 (incisors, canines. Premolars, molars maxillary/mandibular hemiarcade). The canines of male great apes are generally larger/longer than in females. Gibbons have proportionately longer canines than great apes, and there is no sexual dimorphism. Deciduous teeth are present in all infant apes. In orangutans, no deciduous teeth are in occlusion at 2 months, but partial occlusion of the deciduous teeth is present by 9 months and by 12 months of age all deciduous teeth are in occlusion (Winkler, 1996). No deciduous teeth are in occlusion at birth in chimpanzees and in the only gorilla studied.

As in the monkeys, the air sacs of apes are laryngeal diverticula. Not all gibbons have air sacs, but in the siamang there is a highly distensible central "gular sac" that is blown up like a balloon during vocalization. Air sacs are large in both chimpanzees and bonobos, but are more voluminous in gorillas and orangutans extending ventrally under the clavicles into the axilla and dorsally around the neck. The air sacs of apes arise primarily from the lateral saccules of the larynx rather than through a ventral ostium at the base of the thyroid cartilage (thyrohyoid membrane) (Riede et al., 2008). Gibbons, chimpanzees and gorillas, but not orangutans, have a small midline hyoid air sac that may give rise to the intraosseous bulla in the body of the hyoid bone (Steele et al., 2013). Other than the hyoid bulla, the air sacs of the great apes are a contiguous space, but septation may develop in chronic air sacculitis. In chimpanzees the lateral extensions are reported to be asymmetrical, but pathologists should confirm this during necropsy (Swindler and Wood, 1982). Air sac lining epithelium is generally ciliated ranging from cuboidal to pseudostratified. Although cilia are present, clearance is limited. The adventitia is well vascularized, fibro-fatty tissue with sparse flat bands of skeletal muscle and nerves. The air sac membrane is closely applied to underlying muscle fascia and to the overlying dermis/hypodermis. Fat often comprises a large proportion of the externally visible, pendulous "throat sac" in orangutans.

Air sacs develop postnatally. In limited studies of chimpanzees and gorillas the small hyoid air sac is the first one to develop while the portions arising from the lateral laryngeal ostia expand rapidly in late infancy (2–5 years in the chimpanzee) (Nishimura et al., 2007). Air sacculitis is reported in all the apes, but is especially problematic in the orangutans.

The thyroid glands of apes can be difficult to find at postmortem especially in obese animals. They sit just below the larynx, and, because of the short neck, are at the thoracic inlet partially underneath the clavicles. They are flattened and shield-shaped, often with a well-defined isthmus.

Lingual tonsils, similar to those found in humans, are present on the dorsal surface of the base of the tongue in chimpanzees and gorillas, but are not yet documented in gibbons and orangutans (Costello et al., 2017). Enlargement of these and the pharyngeal tonsils can lead to difficulty in intubation for anesthesia.

Submandibular and parotid salivary glands are usually quite prominent. Acinar cells of serous salivary glands have abundant eosinophilic to amphophilic granules. Goblet cells are abundant in the ducts. Salivary gland can be mistaken histologically for pancreas.

Regional Thoracic Anatomy

In all great apes but the orangutan, the right lung has three lobes and the left lung has two lobes. In the orangutan there is one lobe on each side (Nakikura, 1992). The white-handed gibbon (and presumably other gibbons), similar to OW monkeys, has 4 lobes on the right, including the accessory lobe and three on the left (Nakikura and Ehara, 1993). The right superior bronchus in apes exits the trachea anterior to the main bifurcation and can be potentially obstructed during intubation leading to mismatching of ventilation and perfusion (Lowenstine and Osborn, 2012).

The position of the heart within the chest is not well defined. In humans the long axis of the heart is at a 30 degree angle to the midline so that the apex points to the left and the right ventricle is in opposition to the diaphragm. This appears also to be the case in chimpanzees and gorillas, but for all apes heart position relative to midline and diaphragm should be noted during necropsy to help acquire the data needed to confirm orientation in health and disease.

The thymus of chimpanzees and orangutans is bilobed and located in the anterior mediastinum overlying the base of the heart. In gorillas and gibbons, a third lobe extends anteriorly up the ventral neck (Straus, 1937).

Urogenital Tract Anatomy

The contour of the kidneys of all apes is smooth without lobation, similar to those of other nonhuman primates, and unlike those of humans (Straus, 1937). Orangutans have a single flat papilla which resembles a renal crest. Pathologists, take note: improved description of renal anatomy is needed.

Male apes all have a prepuce and a baculum or "os penis." The relative size of the penis, presence and shape of the glands penis, and the presence of spines is highly variable and depends on breeding strategy, female anatomy and degree of perineal swelling during the receptive stage (Dixson, 2012).

Testicles are relatively larger in apes with multimale breeding strategies to facilitate sperm competition (Harcourt et al., 1981). Testicles of the common chimp are very large in proportion to body size with a combined volume of 121.7 ± 94.5 mL, while those of gorillas are quite small (combined volume 7.7 ± 2.9 mL) and orangutans are intermediate (combined volume 27.7 ± 11.9 mL) (Fujii-Hanamoto et al., 2011). Microscopically, gorilla testes are characterized by abundant interstitial (Leydig) cells, and tubules with thin seminiferous epithelium. In contrast the seminiferous epithelium of chimpanzees is much thicker, the seminiferous tubules are in close apposition, and the scant interstitium contains only sparse numbers of interstitial cells. In orangutans the histology is intermediate between gorillas and chimpanzees. The distinctive appearance of gorilla testes is present even in free-living mountain gorilla dominant silverback males dying acutely from trauma, suggesting, as was previously hypothesized by Foster and Rowley (1982), that the appearance is within normal limits and is not an indicator of infertility or atrophy as purported by earlier authors.

Male accessory sex glands include prostate, seminal vesicles, and bulbourethral glands. The seminal vesicles and prostate of chimpanzees are relatively large, while those in gorillas and orangutans are smaller. Prostatic mass in one 32-year-old gorilla was 15 g (Jacobs et al., 1984). Prostatic hyperplasia and seminal vesicle dilation are described in older chimpanzees (Chaffee et al., 2016; Steiner et al., 1999). The great apes all have human prostate-specific antigen (PSA)-like gene and immunohistochemistry using anti-PSA antibodies demonstrate the antigen in gorilla and chimpanzee prostatic epithelium (Karr et al., 1995). More attention to male accessory sex glands needs to be paid at necropsy to better define normal parameters and pathological lesions.

Female Reproductive System

The ovaries of infant female apes are small, flat, wrinkled, and replete with myriads of primary oocytes/primordial follicles, the numbers of which dramatically decline during the last trimester of gestation and further decrease during reproductive years due to atresia and ovulation (Cloutier et al., 2015). Primary follicles are concentrated in the outer cortex. Resting ovaries of adult gorillas are gray and flat with a creased or folded surface. There is no ovarian bursa in any ape species. Great ape ovaries, resemble those of women histologically, but ovaries of gibbons have interstitial gland tissue (Mossman and Duke, 1973).

All apes have a uterus simplex that is pear-shaped and flattened ventrodorsally. Fallopian tubes are tortuous and often folded back onto the uterine body. All apes menstruate. Cycle lengths and other reproductive parameters are listed in the Supplemental Materials Table e2.

Placentation in all the apes is monodiscoid, hemochorial and villous (Benirschke, 2017; Carter, 2007, 2011; Carter et al., 2015; Carter and Pijnenborg 2011, 2016; Soma, 1983). Implantation is invasive/interstitial and covered by maternally derived "decidua capillaries," similar to humans, but distinct from the superficial implantation of OW monkey (Crosley et al., 2013; Pijnenborg et al., 2011a,b). Extraplacental membranes are generally circummarginate and consist of the translucent chorioamnion. There is no allantoic cavity at term. Normal umbilical cord lengths are not yet established, but, according to Benirschke, umbilical cords of bonobos (>70 cm) and gorillas (>65 to over 100 cm) are unusually long compared to humans (average 55 cm). Umbilical cord lengths for orangutans ranged from 40 to 75 cm and attachment was often central rather than marginate as in the other apes (see also Supplemental Materials Table e2). Elongated umbilical cords can develop knots and cause fetal strangulation. Short cords can limit fetal mobility leading to contractures. Whenever possible placentas should be examined from all ape births and a protocol for fetal and placental post mortems is included in great ape necropsy protocol available on the AAZV website (http://www.aazv.org/?page=42).

Gastrointestinal Tract

The esophagus is lined with stratified squamous epithelium with abundant mucous glands. In the mountain gorilla, the muscularis of the distal approximately one-fourth is smooth muscle, while that of the middle is mixed and the upper portion is striated muscle, similar to humans. This needs to be characterized in other apes. All apes have a simple stomach which is elongated (chimpanzee) to globular (orangutan). Histologically there is a limited region of cardiac glands around the gastroesophageal junction, a body of stomach with proper gastric glands and a large pyloric region (Stevens and Hume, 1995). Pyloric glands are rich in mucous cells and sections can be confused with colon histologically. However, colonic glands have no coiling or branching of the crypts and colonic surface epithelium is cuboidal rather than columnar. The duodenum is "s" shaped. The proximal duodenum contains abundant Brunner's lands (especially in gorillas) (Krause, 1975). Paneth cells are present in small intestinal crypts. The length of the small intestine is proportionately longer in orangutans than chimpanzees, as is the length and volume of the colon and cecum. Gorillas have the most capacious large intestine of all the apes in keeping with a high degree of follivory. All apes have taenia (bands) and haustra (saccules) in the large intestine and

diverticulosis and diverticulitis of the haustra can occur. All apes have a vermiform appendix which is particularly long in the orangutan. Histologically it is endowed with abundant gut-associated lymphoid tissues (GALT) which diminishes with age (Fisher, 2000; Scott, 1980; Smith et al., 2009).

Central Nervous System and Pituitary and Adrenal Glands

There are several resources for anatomy of the brain of apes, especially chimpanzees (www.**chimpanzeebrain**.org/). The cerebellum is relatively large and the vermis varies from well-developed in chimps and gibbons to reduced in gorillas and markedly reduced or absent in orangutans (Matano and Hirasaki, 1997). The axis of the brain stem is bent at the level of the midbrain. This must be taken into account making transverse (coronal sections) of the brain. A guide for trimming macaque brains can be used as an aid in sectioning ape brains (Pardo et al., 2012). The major lobation is similar in great apes and humans and topology has been studied using MRI (Semendeferi and Damasto, 2000). The temporal lobes of the cerebral cortices are well developed and separated from the rest of the cerebral cortex by a deep Sylvian fissure (*Sulcus lateralis*), and the cerebral cortices contain many gyrations. The average brain mass of an adult chimpanzee is 381.7 ± 37.2 g and that of a neonate 150.9 ± 17 (DeSilva and Lesnik, 2006). Normal brain weights and brain/body weight rations need to be better documented in all the apes.

The end of the spinal cord (conus medullaris) lies at L1-2 in humans. Its location in all the apes needs to be determined. In MRI images from one gorilla, only the cauda equine was seen at L3 (Aryan et al., 2006).

Apes, like humans, lack a pars intermedia. The gland is divided in to a central portion and two lobes or "wings" (Rasmussen and Rasmussen, 1952).

Grossly, adrenal glands of the great apes are flattened and convoluted with in-folding of the cortex. Cross sections do not always contain medulla, grossly or histologically. As in all catarrhine primates, there is a fetal cortex that involutes postnatally and is replaced by the three zones of the definitive cortex (Parker et al., 2014). In gorillas and orangutans, the zona glomerulosa is discontinuous and the zona reticularis often contains dark brown to black granular pigment, which special stains reveal to be ceroid/lipofuscin.

ADDITIONAL VIRUSES AND VIRAL DIVERSITY IN APES

Virus discovery in the apes has expanded in the molecular era with the advent of nucleic acid amplification techniques and next generation sequencing. Early knowledge of ape viruses relied on solely on serosurveys, detection of viruses via histopathology and ultrastructure, and/or virus isolation in cell culture (all of which are still useful in the molecular era) (Kalter, 1969; Soike et al., 1969 a,b, 1971). A large number of virus have been identified, but many viruses went undetected or uncharacterized because they could not be grown in cell cultures. Modern sensitive techniques allow for detection of minute amounts of viral nucleic acid in samples, such as feces, urine, and saliva (Gillespe et al 2008; Smiley-Evans et al 2016). Not only has this allowed identification of novel viruses, but it has also proved valuable for epidemiological studies. Caution must be exercised; however, because some of these sequences, especially those in feces, may be of prey item origin as chimpanzees and to a lesser extent in bonobos and orangutans are known to prey on other mammalian species including primates (De Nys et al 2015). The presence of viral nucleic acid also does not mean that the agent is causing disease. Virus discovery is often reported without accompanying clinical or anatomic pathological confirmation of associated lesions or location of virus replication. Likewise, seropositivity indicates exposure significant enough to cause seroconversion, but does not indicate ability of the agent to actually cause disease in the species. This means that the significance to ape health of many of the detected viruses remains uncertain. The virus infections of apes that have been associated with clinical illness and/or confirmed lesions have been covered in the text. Table e3 is a compilation of viruses of uncertain pathogenicity that have been identified in apes.

ADDITIONAL PARASITES OF APES

There have been many coprological studies in apes that have identified numerous parasites for which evidence of pathogenicity is often lacking (Table e4).

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TABLE e1 The Apes: Scientific and Common Names, Geographic Distribution, Conservation Status

Scientific Name	Common Names	Geographic Range	IUCN Status
Gibbons			
Hylobates lar (4 or 5 subspecies)	White-handed, lar or common gibbon*	Widely distributed in Southeast Asia, Indonesia, Malaysia, Myanmar, Thailand, Sumatra	EN
H. agilis (2 subspecies)	Black-handed or agile gibbon*	Sumatra, Malaysia, Southern Thailand	EN
H. muelleri (3 subspecies)	Mueller'sor gray gibbon*	Borneo	EN
H. albibarbis	White-bearded or Bornean agile gibbon	Borneo	EN
H. moloch (2 subspecies)	Javan silvery gibbon*	Java	EN
H. piliatus	Pileated or capped gibbon*	Java	EN
H. klossii	Kloss's or Mentawai gibbon*	Mentawai	
Hoolock hoolock	Western hoolock	Assam, Mizoram, Bangladesh, Myanmar	EN
H. leuconedys	Eastern hoolock*	Southern China, Myanmar	VU
Symphalangus syndactylus	Siamangs*	Sumatra, Malay peninsula	EN
Nomascus concolor (4 subspecies)	Black crested gibbon	China, Laos, northern Vietnam	CR
N. leucogyns	Northern white-cheeked gibbon*	Northern Vietnam, northern Laos	CR
N. gabriellae	Gabriell's, yellow-cheeked or buff-cheeked crested gibbon*	Vietnam, Laos, Cambodia	EN
N. hainanus	Hainan gibbon	Hainan Island, China	CR
N. nasutus	Cao-Vit or eastern black crested gibbon	Southeast China, North Vietnam	CR
N. siki	Southern white-cheeked crested gibbon*	Laos, Vietnam	EN
Orangutans			
Pongo abelii	Sumatran orangutan*	Sumatra	CR
Pongo tapanuliensis	Tapanuli oranutan	Sumatra	CR
Pongo pygmaeus (3 subspecies)	Bornean orangutan*	Borneo: Malaysia, Indonesia	CR
Chimpanzees			
	Common chimpanzees*		
Pan troglodytes troglodytes	Central chimpanzee or tschengo*	Cameroon, Gabon, Republic of Congo	EN
P. t. schwein furthii	Eastern or East African chimpanzee*	Central African Republic, Democratic Republic of Congo, Sudan, Tanzania, Uganda, Burundi, Rwanda	EN
P. t. ellioti (vellerosus)	Nigeria-Cameroon chimpanzee	Nigeria, Cameroon	EN—may be upgraded to CR
P. t. versus	West African (Western) chimpanzee*	Cote d'Ivoire, Liberia, Guinea, Sierra Leon	EN
Bonobo or pygmy chimpanzee			
Pan paniscus	Bonobo*	Democratic Republic of Congo	EN
Gorillas			
	Western Gorillas		
Gorilla gorilla gorilla	Western lowland gorilla*	Angola, Cameroon, Central African Republic, Congo, Gabon, Equatorial Guinea	CR
G. g. dehlei	Cross river gorilla	Nigeria-Cameroon border	CR
	Eastern Gorillas		
Gorilla beringei beringei	Mountain gorilla	Virunga massif (Rwanda, Democratic Republic of Congo, Uganda) and Bwindi (Uganda)	CR
G. b. graueri	Eastern lowland or Grauer's gorilla	Democratic Republic of Congo	CR

EN, Endangered; CR, critically endangered.
* Held in zoos.
Source: Adapted from IUCN Red List, IUCN Red List Designations

TABLE e2 Reproductive Parameters for the Apes

	Gibbons (*H. lar*)	Orangutans[a]	Bonobos	Chimpanzees	Gorillas[b]	References
Female age at sexual maturity (puberty) (estimated years)	6–7	12-(wild) 6–7 (captive)	>5	>10	6 8 (Gbb)	Hodgkiss et al. (2010); Shumaker et al. (2008); Wich et al. (2004); Harcourt et al. (1980)
Male age at puberty (estimated years)	6–9	8–15	8–10	10–10		Behringer et al. (2014); Cawthon Lang, 2005, Breznock et al., 1977
Menstrual cycle length (days)	22–44 (colony) 23.1 ± 1.1 (zoos)	28–32 (captive)	45 (captive)	37 (captive)	30–33 days 29 ± 4 (wild)	Breznock et al. (1977); Rafacz et al. (2013); Benirshcke (2016); DeWaal and Lanting (1997); Habumuremyi (2016); Nadler (2008)
Age at first birth (years)	11	13–18 (wild) 7 captive	13–14 years	15.5 year Gombe	8 (Ggg)–10 (Gbb)	Barelli et al., 2007 Schumaker et al. (2008)
Gestation (days)	180–210 191 ± 7	227–301	208–237	226.8 ± 13.3	257 254 (Gbb)	Gavan (1952); Drews et al. (2011); Huang et al. (2013); Rafacz (2013)
Birthweight (g)	368 *lar* group; 540 *concolor* group; 551 *Symphalagus*	15,000 –2,300	1270	1800 range 1130 to 2370 (colony)	1396 and 3058 (2200 avg.)	Gavan (1952); Cawthon Lang (2005, 2006, 2010); Geissmann and Orgeldinger (1995); Library@sandiegozoo.org
Interbirth interval (years)	3.5	7–8 (B—wild) 9.3 (S—wild)	4–6	3–5	4.2 ± 1/3 (zoo Ggg) 5.6 ±1.5 (wild Gg) 3.2–6.1 (Gbb)	Pin wisc; Library.sdzoo.org; Stoinski et al. (2013); DeWaal and Lanting (1997)
Age at weaning (years)	2.5 (*N. concolor*)	5–8	4–5	4–6	3–4 y 3.4–5.7 (3.8 av) (zoo Ggg) 1.8–5.2 (Gbb)	Huang et al. (2013); Kuroda et al. (1989); Cawthon Lang (2005, 2006, 2010); Stoinski et al. (2013); Library@sandiegozoo.org
Placental weight (g)	Not described	B: 266–430 (avg. 300) S: 290–380 (avg. 320)	68 (partial?); 185 (fixed)	150–375 (avg. 259)	350	Benirschke (2016); Soma (1983)
Umbilical cord length (cm)	Not described	B: 55–72 cm S: 28–60 cm	73–76 cm	S: 38–80 cm	100 cm	Benirschke (2016); Soma (1983)

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TABLE e2 Reproductive Parameters for the Apes (*Cont.*)

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Gorillas: Ggg (Gorilla gorillagorilla, western lowland gorilla), Gbb (Gorilla beringei beringei) mountain gorilla.

TABLE e3 Ape Viruses of Undetermined Pathogenicity

Virus	Host Species	Specimen	References
Roseoloviruses (Betaherpesvirus)	Chimpanzees, bonobos, gorillas	Blood	Lavergne et al. (2014)
Cytomegaloviruses (Betaherpesviruses)	Chimpanzees, gorillas, orangutans	Detected in blood and various tissues	Leendertz et al (2009)
Lymphocryptoviruses (Gamma-1 herpesviruses)	All apes	Detected in feces, blood or tissues; serology	Kilbourn et al. (2003); Phakdeewirot et al. (2006); Ehlers et al. (2010); Yoshida et al. (2016)
Rhadinoviruses (Gamma 2 herpesviruses)	Chimpanzees, gorillas, gibbons, orangutans	Detected in buffy coats; serology	Lacoste et al. (2000); Duprez et al. (2004); Mugisha et al. (2010)
Polyomaviruses (Merkel cell type); BK and JC-like; PtrovPyV8; BK-like	Bonobos, gorillas, chimpanzees, Orangutans	Detected in feces; Detected in tissues	Deuzing et al. (2010); Groenewoud et al. (2010); Leendertz et al. (2011); Nicol et al. (2014); Madinda et al. (2015, 2016); Ben Salem et al. (2016); van Persie et al. (2016)
Adenoviruses	Chimpanzees, gorillas, orangutans	Detected in feces	Kilbourn et al. (2003); Wevers et al. (2011); Duncan et al. (2013); Hoppe et al. (2015); Nikogue et al. (2016); Dadáková et al. (2017)
Adeno-associated parvoviruses	Chimpanzees	Serology	Calcedo and Wilson 2016
Parvovirus-4 like "Partetraviruses" and B19-like parvoviruses	Chimpanzees, gorillas	Detected in plasma or feces	Sharp et al. (2010)
Boca(parvo)viruses	Chimpanzees, gorillas	Detected in feces; Possible association with diarrhea(gorillas)	Kapoor et al. (2010); Brožová et al. (2016); Nze-Nkogue et al. (2017)
Gokushoviruses (ssDNA phage-like)	Chimpanzees	Detected in feces	Walters et al. (2017)
Circo-like ssDNA viruses	Chimpanzees	Detected in feces	Blinkova et al. (2010)
Hepatitis E virus (*Hepiviridae*)	Bonobos, gorilla, lar gibbon	Serology	Spahr et al (2018)
Enteroviruses	Chimpanzees, Gorillas	Detected in feces; serology	Harvala et al. (2012); Sadeuh-Mba et al. (2014); Mombo et al. (2017)
Saliviruses (*Picornaviridae*)	Chimpanzees	Detected in feces	Reuter et al. (2017)
Sapoviruses (Caliciviruses)	Chimpanzees	Detected in feces	Mombo et al. (2014)
Caliciviruses	Bonobos, gorilla	Serology, Isolation from an oral vesicle (bonobo), spleen (gorilla)	Smith et al. (1983, 1985)
Rotaviruses (SA-11-like)	Orangutans, gorillas, chimpanzees	Serology; Detected in feces (electron microscopy); Possible association with diarrhea	Ashley et al. (1978); Kilbourn et al. (2003)
Coronaviruses	Chimpanzees	Detected in feces asymptomatic chimpanzees (electron microscopy)	Ashley et al. (1978)
Foamy viruses (*Retroviridae, Spumavirinae*)	All apes	Tissues, blood, plasma, saliva	Bieniasz et al. (1995); Hussain et al. (2003); Verschoor et al. (2004); Liu et al. (2008); Peeters and Delaporte (2012)
STLV-1,2	Chimpanzees, bonobos	Virus isolation; Detection in blood, tissues	van Brussel et al. (1998); Junglen et al. (2010)
Endogenous retroviruses	Chimpanzees, bonobos, gorillas	Genome interrogation	Barbulescu et al. (2001); Mun et al. (2014)
Arboviruses (alphaviruses and flaviviruses)	Orangutans, gorillas	Serology	Kilbourn et al. (2003); Kading et al. (2013)

(*Continued*)

TABLE e3 Ape Viruses of Undetermined Pathogenicity (*Cont.*)

Virus	Host Species	Specimen	References
Dengue virus	Orangutans	Serology	Kilbourn et al. (2003)
Japanese encephalitis virus	Orangutans	Serology	Kilbourn et al. (2003)
Zika virus	Orangutans	Serology	Kilbourn et al. (2003)
Legat virus	Orangutans	Serology	Kilbourn et al. (2003)
Sinbis virus	Orangutans	Serology	Kilbourn et al. (2003)
Tembusu	Orangutans	Serology	Kilbourn et al. (2003)

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TABLE e4 Parasites of Apes

Parasite	Species in Which Reported	Organ System	Pathogenicity/Lesions	References
NEMATODES				
Enterobius spp. *(E. anthropopitheci)*	Chimpanzees	Cecum, appendix, colon	Apathogenic	Flynn (1974)
Enterobius vermicularis	Chimpanzees	Distal colon	Invasive in chimpanzees; colitis, proctitis, draining tracts in perineum; can be fatal	Yaguchi et al. (2014)
Lemuricola pongoi) Pongobius hugot Pongobius foitovae Enterobius buckleyi	Orangutans	Intestines	Typical pin worms	Foitova et al. (2014); Kuze et al. (2010)
Probstmayria spp.	Mountain gorillas, chimpanzees	Intestines, especially large intestine	Apathogenic (?)	Sleeman et al. (2000); Rothman et al. (2008)
Chitwoodspirura spp. *(C. serrata, C. wehri)*	Gorillas	Stomach	Unknown	Chabaud and Rousselot (1956), Jamaguti (1961)
Streptopharagus sp. *S. pigmentatus*	Chimpanzee (lab); Gibbons (wild)	Stomach	Not reported	Barelli and Huffman (2017)
Trichurids (whipworms)	Gorillas, orangutans	Cecum (presumptive)	Not reported	Freeman et al. (2004); Nuracahyo et al. (2017)
Capillaria brochieri Capillaria sp.	Bonobos	Intestines	Diarrhea	Justine (1968); Narat et al. (2015)
Capillaria hepatica	Gorillas, chimpanzees	Liver	Parasite migration tracks with ova and variable inflammation	Graczyk et al. (2001); Myer and Kkuntz (1972)
Anatrichosoma sp.	Gibbons	Skin, ears, lips, nostrils, eyelids	Nodules, acanthosis with intraepidermal parasitic cysts	Breznock and Pullen (1975)
Strongyloides fuellborni S. stercoralis	All apes	Small intestine (adult females), colon (larvae), developing larvae migrate through lymphatics and lungs	Often asymptomatic, but can cause enterocolitis; hyperinfections with *S. stercoralis* can cause severe enterocolitis, pulmonary hemorrhage and pneumonia and can be fatal	Labes et al. (2011); Lowenstine et al. (2008); DePaoli and Johnsen (1978)
Trichostrongyles (unspeciated)	Gorillas, orangutans	Stomach (gorillas)	Chronic gastritis (gorillas)	Muhangi (2008)
Hyostrongylus kigeziensis	Mountain gorilla	Stomach	Chronic gastritis, ulceration, small red worms visible grossly	Rothman et al. (2008)
Paralibyostrongylus kalinae	Mountain gorilla	Stomach	Gastritis with grossly visible red worms	Rothman et al. (2008)
Oesophagostomum blanchardi	Gibbons, orangutans	Colon	Not described, presumed nodules	Nurcahyo et al. (2017)
Oesophagostomum sp. *O. stephanostomum*	Gorillas, chimpanzees	Large intestine	Colitis, mural, and serosal nodules, mucosal ulcers overlying the nodules, asymptomatic to fatal, mucoid diarrhea ± blood	Rothman (2008); Terio et al. (2016); Krief et al. (2008)

Ternidens deminutus	Chimpanzees, gorillas	Large intestine	Mural nodules NOTE: some cases may be mis-identification due to similarity of eggs to those of other strongyles especially *Oesophagostomum*	Flynn (1974)
Murshididia devians	Mountain gorillas	Colon, maybe small intestine and extraintestinal	A cyanthostome strongyle with likely tissue invasion/ migration	Rothman et al. (2008)
Necator spp. (hookworms)	Chimpanzees, gorillas	Intestines	None described	Hasagawa et al. (2017)
Abbreviata (Physaloptera) caucasia	Orangutans	Esophagus, stomach, small intestine	None described	Flynn (1974)
Ascaris sp. or *A. lumbricoides*	Gorillas, orangutans, gibbons	Intestines	Usually asymptomatic, worms visible grossly	Kalema-Zikusoka et al. (2005); Nurcahyo et al. (2017); Xie et al. (2013)
Baylisascaris sp.	Orangutan	Brain, visceral larval migrans	Necrotizing encephalitis	Hanley et al. (2006)
Angiostrongylus cantonensis	Gibbons	Lungs, brain, larval migrans	Pulmonary vasculitis with luminal nematodes, eosinophilic necrotizing meningoencephalitis, and myelitis with intralesional nematodes	Gardiner et al. (1990); Duffy et al. (2004)
Parastrongylus costaricensis	Gibbons	Peritoneal cavity, mesenteries, visceral larval migrans	Nodules and masses associated with intestinal walls and mesenteries, granulomatous inflammation around eggs and larvae; adults in mesenteric vessels	Miller et al. (2006)
Fillarids (several species)	Gorillas	Subcutis	Microfilaremia	Vandenberghe et al. (1964)
Dirofilaria pongoi	Orangutans, gibbons	Subcutis, muscles, right ventricle	Microfilaremia	Nurcahyo et al. (2017)
Dipetlonemia perstans	Chimpanzees, gorillas	Subcutis, abdominal cavity	Microfilaremia, vasculitis	Flynn (1974)
Dipetlonemia vanhoofi	Chimpanzees, gorillas	Peritoneal cavity	Microfilaremia, peritoneal nodules	Flynn (1974)
Dipetalonema rodhami	Chimpanzees	Subcutis, peritoneum	Microfilaremia	Flynn (1974)
Dipetalonema gorillae	Gorillas	Subcutis?	Microfilaremia	Vandenberghe et al (1964)
Dipetalonema (Mansonella) strepticerca	Chimpanzees, gorillas	Subcutis, lymphatics, peritoneum	Microfilaremia, edema (?)	Flynn (1974); Bain et al. (1995)
Loa loa	Gorillas	Subcutis	Microfilaremia	Bain et al. (1995)
Moniliformis moniliformis (acanthocephalan)	Chimpanzee	Small intestine	Not described	Flynn (1974); Myers and Kuntz (1972)
Prostenorichis (acanthocephalans)	Orangutans	Intestines	Lesions not described	Nurcahyo et al. (2017)
Mammomonogamus sp. (syngamid)	Western lowland gorillas, orangutans	Respiratory (trachea) (presumptive in gorillas)	Unknown in gorillas Worms grossly visible in trachea of orangutans, causing suffocation	Cerena et al. (2017); Foitová et al. (2008)

(*Continued*)

TABLE e4 Parasites of Apes (*Cont.*)

Parasite	Species in Which Reported	Organ System	Pathogenicity/Lesions	References
TREMATODES				
Schistosoma mansoni	Chimpanzees, gorillas	Intestinal veins, abdominal veins	Liver fibrosis in chimpanzees	Standley et al. (2014)
Schistosoma hematobium	Chimpanzees, gibbons (experimental)	Pelvic and mesenteric veins	Bladder calcification, bladder papillomas, urinary obstruction	Cheever and Duvall (1981); Kuntz et al. (1978)
Dicrocoelium sp.	Orangutans Chimpanzees	Bile ducts	Lesions not reported	Nurcahyo et al. (2017); Kouassi et al. (2015)
Platynosomum fastosum	Orangutans	Bile ducts	Bile duct "damage," mild hepatitis	Warren et al. (1998)
Eurytrema satoi	Gorillas	Bile ducts, pancreas	Lesions not described	Cosgrove (1966); Fiennes (1967)
CESTODES				
Echinococcus granulosa *E. multilocularis*	Gorillas, other apes (?)	Abdominal cavity, disseminated (larval cestodiasis)	Hydatid disease; Visceral uni- or multiloculated parasitic cysts, effusive peritonitis, dissemination to liver, occasionally brain; chronic infection	Benirschke and Adams (1980); Rehmann et al. (2003)
Taenia spp.	Gibbons	Brain, viscera (larval cestodiasis)	Cysticercosis, single cysts in brain or viscera	Sagartz and Tingpalapong (1974)
Versteria sp.	Orangutan	Liver, other viscera including lung (larval cestodiasis)	Unusual parasitic cysts with multinucleated protoplasmic bodies; liver and other viscera, fatal infection (single case)	Goldberg et al. (2014)
Bertiella satyri	Orangutan	Intestines	Asymptomatic (?)	Nurcahyo et al. (2017)
Bertiella sp. *Bertiella studeri*	Chimpanzees	Intestines	Asymptomatic (?)	McLennan et al. (2017)
Anaplocephala gorillae	Gorillas	Jejunum and large intestine at necropsy	Asymptomatic (?); very heavy burdens in geriatric gorillas	Rothman (2008)
Hymenolepis	Orangutan	Intestines	Unknown	Flynn (1974)
PROTOZOA				
Trypanosoma brucei	Chimpanzees	Blood Detected in liver, spleen and feces by PCR	Asymptomatic natural infections ± parasitemia; fatal experimental infection with *T. b. rhodesiense* and *T. b. brucei*, anemia, thrombocytopenia	Jirku et al. (2015)
Trypanosoma cruzi	Chimpanzees, gibbons	Heart	Myocarditis with amastigote forms in cardiac myofibers	Bommineni et al. (2009)
Giardia sp.	Gorillas, gibbons, chimpanzees, orangutans	Upper intestines	Diarrhea and vomiting in zoo animals; often asymptomatic	Nizeyi et al. (1999); Hogan et al. (2014); Debenham et al. (2015); Renquist et al. (1987)
Tetratrichomonas sp.	Chimpanzees	Intestines	Detected in feces, no lesions described	Rushmore et al. (2015)
Pentatrichomonas hominis	Chimpanzees	Intestines	Detected in feces, no lesions described	Smejkalova et al. (2012)

Cryptosporidium sp. *C. parvum*	Chimpanzees, gorillas, orangutans	Intestines	Usually asymptomatic, not readily detected post mortem because of usual long postmortem interval in wild apes	Graczyk et al. (2001); Nyzeyi et al. (1999); Gonzalez-Moreno et al. (2013); Debenham et al. (2015); Parsons et al. (2015)
Cyclospora sp.	Chimpanzees	Intestines	Usually asymptomatic	Smith et al. (1996); Marangi et al. (2015)
Blastocystis spp.	Chimpanzees, gorillas, orangutans	Intestines	Commensal (?)	Drakulovski et al. (2014); Nurcahyo et al. (2017)
Balantidium (Neobalantidiium) coli	All apes	Colon, cecum	Asymptomatic to florid ulcerative and hemorrhagic colitis; sometimes fatal	Teare and Loomis (1982); Lee et al. (1990); Kilbourne et al. (2003); Lankester et al. (2008); Pomajbíková et al. (2013)
Gorilloflasca africana	Gorillas	Intestines	Entodiniomorphid ciliate commensal	Ito et al. (2017)
Prototapirella spp.	Gorillas	Intestines	Entodiniomorphid ciliate commensal	Ito et al. (2016)
Tetratrichomonas sp.	Chimpanzees	Intestines	Detected in feces	Rushmore et al. (2015)
Pentatrichomonas hominis	Chimpanzees	Intestines	Detected in feces	Smejkalova et al. (2012)
Iodamoeba butschlii	Gorillas	Intestines	Detected in feces	Rothman (2008); Sleeeman et al. (2000)
Troglodytella sp.	Chimpanzees, bonobos, gorillas, siamangs	Intestines	Entodiniomorphid ciliate commensal	Pomajbíková et al. (2010); O'Donoghue et al. (1993)
Troglocorys cava	Chimpanzees	Intestines	Entodiniomorphid ciliate commensal	Tokiwa et al. (2010)
Chilomastix mesnelii *Chilomastix* sp.	Orangutans Mountain gorillas	Intestines	Commensal	Foitova et al. (2017); Sleeman et al. (2000)
Endolimax nana	Orangutans	Intestines	Commensal	Foitova et al. (2017)
Entamoeba spp. *E. fragilis* *E. dispar*	Chimpanzees, gorillas, gibbons All apes	Intestines/colon Colon	Usually asymptomatic *E. fragilis*: irritable bowel-like syndrome in gorillas Asymptomatic, occasional diarrhea in gorillas (can be confused with *E. histolytica*)	JirkůPomajbíková et al. (2016); Li et al. (2017); Lankester et al. (2010); Tachibana et al. (2000)
Entamoeba histolytica	All apes	Colon	Often asymptomatic; Ulcerative colitis, liver, and lung abscesses (chimpanzees)	Miller and Bray (1966); Schmidt (1975)
Balamuthia mandrillaris	Gibbons, orangutans, gorillas	Brain and systemic involving visceral organs, lymph nodes	Meningoencephalitis, necrotizing to granulomatous inflammation in CNS and visceral organs	Canfield et al. (1997); Rideout et al. (1997); Gjeltema et al. (2016)

(*Continued*)

TABLE e4 Parasites of Apes (*Cont.*)

Parasite	Species in Which Reported	Organ System	Pathogenicity/Lesions	References
ARTHROPODS				
Amblyoma sp. (Ticks)	Chimpanzees	Nostrils	Grossly visible	Hamer et al. (2013)
Sarcoptes scabei	Chimpanzees, gorillas	Skin, epidermis	Mange, alopecia, pruritis, can be fatal in infant apes; hyperkeratosis with mites in deep epidermal tunnels	Kalema-Zikusoka et al. (2002); Graczyk et al. (2001); Williams et al. (2008)
Pangorillalges gorillae	Gorillas	Skin, epidermis	Mange with alopecia and pruritis; hyperkeratosis with mites in stratum corneal tunnels	Nutter et al. (2005)
Psorergates sp.	Gibbons	Skin	Mange	Atkins et al. (2008)
Demodex–like mites	Gorillas	Skin, sebaceous gland ducts	Incidental histological finding	Lowenstine et al. (2008)
Pneumonyssus oudemansi	Chimpanzees, gorillas	Bronchi and lungs	Lesions not described	Fain (1957)
Rhinophagia pongicola	Orangutan	Frontal sinuses	Lesions not described	Fain (1958)
Pthirus gorillae	Gorillas	Haired skin, entire body	Pediculosis; nits, and adult lice visible grossly	Reed et al. (2007)
Pediculus schaeffi	Chimpanzees	Haired skin	Pediculosis, nits, and adult lice visible grossly	Herd et al. (2015)

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TABLE e4 Parasites of Apes (*Cont.*)

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