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Pathology and Immunohistochemistry of Callitrichid Hepatitis, an Emerging Disease of Captive New World Primates Caused by Lymphocytic Choriomeningitis Virus

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Callitrichid hepatitis is an arenavirus infection that recently emerged as a highly fatal disease of New World primates in the Callitrichidae family. As we previously reported, these primates develop hepatitis after contact with mice that are infected with variants of LCMV ($LCMV_{CH}$), recently determined to have 86% identity with GC-P gene of the Armstrong and Western strains of LCMV. Here, we describe the histopathological lesions and tissue localization of viral antigens in confirmed cases of callitrichid hepatitis from recent outbreaks in two U.S. zoos. The liver in marmosets and tamarins with fatal infections consistently showed degeneration, necrosis, and inflammation, with variable involvement of the spleen, lymph nodes, adrenal glands, intestine, pancreas, and central nervous system. Lymphocytic choriomeningitis virus antigens were identified immunohistochemically in necrotic foci in these organs as well as in nondegenerating areas in lungs, kidneys, urinary bladder, brain, and testes. The multi-organ tropism and histological pattern of LCMV infection in marmosets and tamarins are similar to those reported for the highly virulent arenavirus that causes Lassa fever in humans. Comparative studies of callitrichid hepatitis and Lassa fever would therefore be mutually beneficial for human and nonhuman primate medicine. (Am J Pathol 1995, 148:1441–1449)

Callitrichid hepatitis (CH) is a highly fatal arenavirus disease of captive marmosets and tamarins, New World primates in the family *Callitrichidae*. Fourteen epizootics of this disease emerged sporadically since the early 1980s at 11 North American zoos. These outbreaks resulted in the deaths of 67 animals.[1–3] We previously demonstrated the viral etiology of CH by experimentally transmitting the disease to common marmosets (*Callithrix jacchus*) using a bacteria-free filtrate of the liver homogenate from a zoo-housed emperor tamarin (*Saguinus imperator*) that died from the natural CH disease.[2] In nonhuman primates, natural outbreaks of CH have been limited to *Callitrichidae* residing in zoos and animal parks with the highest fatality rate in the endangered golden lion tamarin (*Leontopithecus rosalia*).[2]

In 1990, the specific etiological agent of CH was identified as an arenavirus related to lymphocytic choriomeningitis virus (LCMV),[4] a zoonotic agent, the principal host of which is the common mouse, *Mus musculus*, and the public health importance of which has received renewed interest.[5] Recently, the GP-C gene of the CH virus was cloned and sequenced, and the cDNA was found to be 84 to 86% identical to those of the GP-C genes of LCMV Armstrong (ARM) and Western (WE) strains.[6] As with other arenaviruses in humans, the epidemiology of LCMV stems from contact with the urine and oral secretions of persistently infected rodents. The majority of human LCMV infections are self-resolving influenza-like illnesses; however, in some individu-

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als, the disease may progress to aseptic meningitis or meningoencephalitis, requiring hospitalization. Rare human deaths have been attributed to LCMV infections with severe pharyngitis, fever, malaise, and bleeding from mucous membranes. The postmortem findings in these deaths of acute pneumonitis, hepatic triaditis, and multiple hemorrhages are reminiscent of Lassa fever, which is responsible for highly fatal outbreaks of hemorrhagic fever in sub-Saharan Africa.[7] Cynomolgus and rhesus monkeys experimentally inoculated with the WE strain of LCMV have viral antigens in many tissues and develop a fatal systemic infection similar to human Lassa fever.[8]

The recent outbreaks of LCMV in zoo primates have been associated with exposure to LCMV-infected mice. We showed that a fatal outbreak of CH in two separate colonies of marmosets and tamarins at a southwestern zoo was associated with a common source of neonatal feed-mice with inapparent LCMV infections. The LCMV that we isolated from the mice and the affected primates that were fed the mice were related to $LCMV_{CH}$ isolates from previous natural outbreaks of CH and to the ARM strain of LCMV, as determined by serological and nucleic acid hybridization assays.[2] However, in this recent outbreak there were some differences in the clinical manifestations and pathological changes from previous zoo outbreaks. Specifically, some of the affected primates exhibited a more protracted clinical course, developed seizures associated with meningoencephalitis, or respiratory distress, and showed a more widespread distribution of lesions in different organs.

In the present study we compare the pathological changes and immunohistochemical findings in experimentally inoculated common marmosets with the changes seen in naturally infected emperor and golden lion tamarins and pygmy marmosets, *Cebuella pygmae*, from previous epizootics of CH. Our findings suggest that either the high virulence of CH in *Callitrichidae* results from LCMV variants present in the mouse carriers that are hepatotropic in callitrichids or that these primates are highly susceptible to many LCMV variants.

Materials and Methods

Tissues

Specimens of liver, brain, heart, kidney, spleen, lung, lymph node, pancreas, adrenal, small and large intestine, stomach, and reproductive tracts were obtained at necropsy from three common marmosets with experimentally induced CH and a naturally infected emperor tamarin that served as the inoculum donor in a previously published study;[2] from three golden lion tamarins and four pygmy marmosets involved in a common source outbreak of CH at the Fort Worth Zoo (FWZ) in Dallas, TX;[3] and from two golden lion tamarins and a pygmy marmoset that died in 1993 in a new episode of CH from the Henry Doorly Zoo (HDZ) in Omaha, NE. Livers from the two HDZ tamarins were positive for LCMV antigens by solid phase immunoassay as previously described; however, the assay of the HDZ marmoset's liver was inconclusive, probably because the liver arrived thawed and dehydrated. Tissues were divided and frozen at −70°C and fixed in 10% buffered formalin. Fixed tissues were routinely processed, embedded in paraffin, sectioned at 5 μm, and stained with hematoxylin and eosin (H&E) for histopathological examination; replicate 5-μm sections were cut for immunohistochemistry for the detection of viral antigens.

Immunohistochemistry

Sections of formalin-fixed, paraffin-embedded tissues from each animal were stained for $LCMV_{CH}$ viral antigens by the labeled avidin-biotin complex method. Briefly, sections were deparaffinized, hydrated to dH_2O, washed in phosphate-buffered saline (PBS; pH 7.4), and digested with 500 μg/ml protease VIII (Sigma Chemical Co., St. Louis, MO) for 15 minutes at 37°C. Sections were incubated with $LCMV_{CH}$-specific guinea pig antiserum (No. 13065; provided by Dr. Peter Jahrling, USAMRIID, Ft. Detrick, Frederick, MD), diluted 1:50, for 1 hour at room temperature. After washing in PBS, sections were incubated with biotinylated goat anti-guinea pig IgG (Vector Laboratories, Burlingame, CA) and diluted 1:200 for 1 hour at room temperature. Sections were washed in PBS, covered with peroxidase-conjugated streptavidin, prepared according to the manufacturer's instructions (P50209, Zymed, San Francisco, CA) for 15 minutes, and washed again in PBS. Finally, sections were flooded with 0.5 mg/ml 3,3′-diaminobenzidine tetrahydrochloride that had been solubilized in $NiCl_2$ buffer (Digene Diagnostics, Silver Spring, MD) as previously described,[9] washed in water, and counterstained with nuclear fast red (Sigma).

Controls included tissues from uninfected marmosets and tamarins incubated with the 13065 primary antiserum as described above, and tissues from infected marmosets and tamarins immunostained either without applying the primary antiserum or by

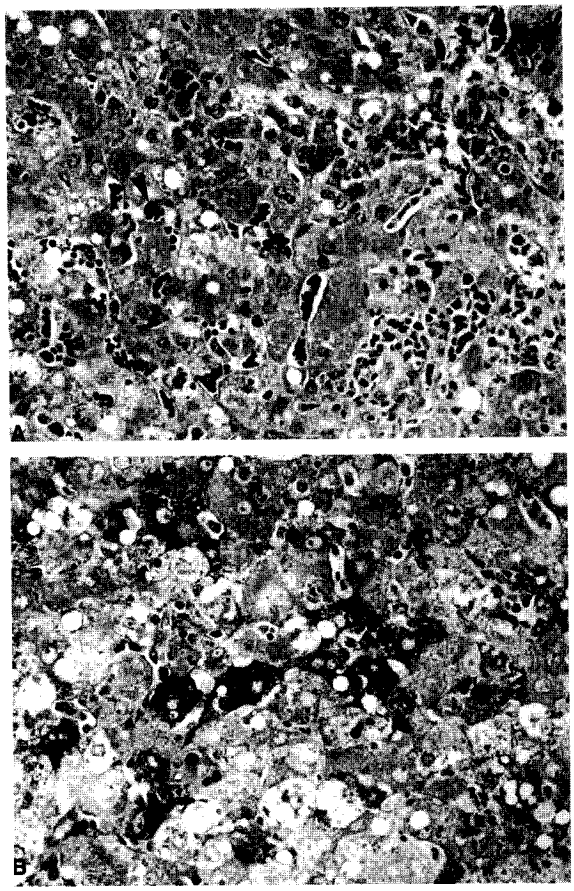

Figure 1. A: *Liver from emperor tamarin with natural occurring callitrichid hepatitis ($LCMV_{CH}$ infection). Hepatic plates are disrupted and contain necrotic hepatocytes, degenerating hepatocytes, and infiltrates of lymphocytes and a few neutrophils. Note acidophilic body* (arrow) *typical of those seen in $LCMV_{CH}$-infected livers.*[1,2] *(magnification, ×300; H&E).* B: *Immunoperoxidase labeling shows $LCMV_{CH}$ viral antigen (dark granular material) mostly in misshapen, abnormal appearing hepatocytes from the same tamarin liver depicted in* A *(magnification, ×300).*

substituting nonimmune guinea pig serum for the primary antiserum. None of these controls showed viral antigens in any of the tissues tested.

Results

Histopathology

Histopathological examination of tissues from the three experimentally infected common marmosets and the naturally infected emperor tamarin and five golden lion tamarins revealed similar virus-induced pathological changes in all three species. These changes included hepatitis characterized by random foci of hepatocellular degeneration and spotty necrosis throughout the liver (Figure 1A). The lesions were often associated with a mild mononuclear inflammatory cell infiltrate with a few neutrophils scattered throughout the lobules. A characteristic finding, although variable in number among individual animals, were round, acidophilic structures that appeared to arise from whole hepatocytes or from cytoplasmic segments. These structures resembled apoptotic (Councilman-like) bodies and were usually free within the sinusoids but also occasionally within Kupffer cells. These changes resembled the liver lesions previously reported as part of the case definition for the original CH outbreaks.[1] Immunoperoxidase staining revealed LCMV antigen primarily in those hepatocytes within and around the the necrotic foci (Figure 1B). Lymphocytic choriomeningitis virus antigen was also present in Kupffer cells and in some hepatocytes that appeared histologically normal by routine staining. In two of the common marmosets, biliary epithelial cells within the portal triads were also antigen positive.

Necrosis also occurred in spleen, abdominal lymph nodes, adrenal cortex, and intestinal tract of the affected tamarins and the common marmosets; however, the necrotic foci were not as prevalent as those in the livers of the same animals. Necrosis in the spleen and lymph nodes primarily involved foci within the centers of follicles. LCMV antigens in the lymphoid tissues were sparse and confined to macrophages and intrafollicular reticular cells; antigen was not detected in lymphocytes proper. In the adrenal glands, small, random necrotic foci of cortical cells were most evident within the zona fasciculata, which stained moderately for LCMV antigens. Antigen staining also occurred randomly in the cytoplasm of non-necrotic cortical cells of the zona fasciculata in all of the affected animals and in the zona glomerulosa of a common marmoset and a golden lion tamarin. Necrotic foci in the intestinal tract were predominantly in the enterocytes and goblet cells of the colonic crypts, which were antigen positive. In one golden lion tamarin, segments of the esophageal squamous epithelium had LCMV antigens within inflamed foci that were verified in replicate H&E sections.

Immunoperoxidase staining of pulmonary tissue revealed LCMV antigens in alveolar macrophages and other cells (fibroblasts or capillary endothelium) within the alveolar walls. Importantly, affected animals of each species also had LCMV antigens evident in some of the bronchiolar lining cells. Renal cortical lesions attributable to LCMV were absent, although two of the three common marmosets and three of the five golden lion tamarins had clusters of LCMV-antigen-containing cells in the proximal tubular epithelium. Variable numbers of glomerular mesangial cells contained viral antigens as well as en-

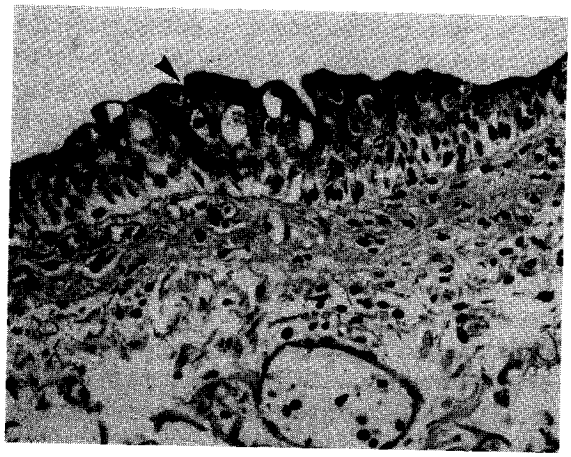

Figure 2. *Urinary bladder from a golden lion tamarin (HDZ) with naturally occuring CH contains $LCMV_{CH}$ antigen in the upper urothelial layer* (arrow), *a possible source of viral shedding. (Magnification, ×300; immunoperoxidase stain).*

dothelial cells adjacent to the collecting duct in the medulla. Foci of intact urothelium from the urinary bladder were also postive for LCMV antigen (Figure 2). LCMV antigens also occurred in testes obtained from two common marmosets but only in some of the Leydig cells, which stained intensely without degenerative changes or inflammation. Two of the three tamarins from the FWZ outbreak with central nervous system signs and two tamarins from the HDZ outbreak showed lymphocytic infiltration of the meninges (Figure 3A) and cerebral perivasculitis associated with mononuclear inflammatory cells. LCMV antigens were limited to epithelial cells of the choroid plexus and to the vascular endothelium (Figure 3B). Neurons and supporting cells in the neuropil did not contain any detectable LCMV antigen.

In contrast to the lesions described for the common marmosets and the emperor and golden lion tamarins, the livers of the five pygmy marmosets (four FWZ and one HDZ), which died 5 to 14 days later than the common marmosets and tamarins, had minimal hepatocellular necrosis but an intense portal mononuclear inflammatory cell infiltration with extension into portal vessels (Figure 4A). The Councilman-like bodies characteristic of the common marmoset and tamarin hepatic lesions were mostly absent in the pygmy marmosets. Nevertheless, LCMV antigens were observed in many hepatocytes throughout the hepatic parenchyma (Figure 4B), and in one animal, antigen was also evident in the biliary epithelium. Likewise, clusters of intact adrenal cortical cells stained positive for LCMV antigens with minimal degenerative changes evident (Figure 5A). Lymphocytic gastritis also occurred in the pygmy marmo-

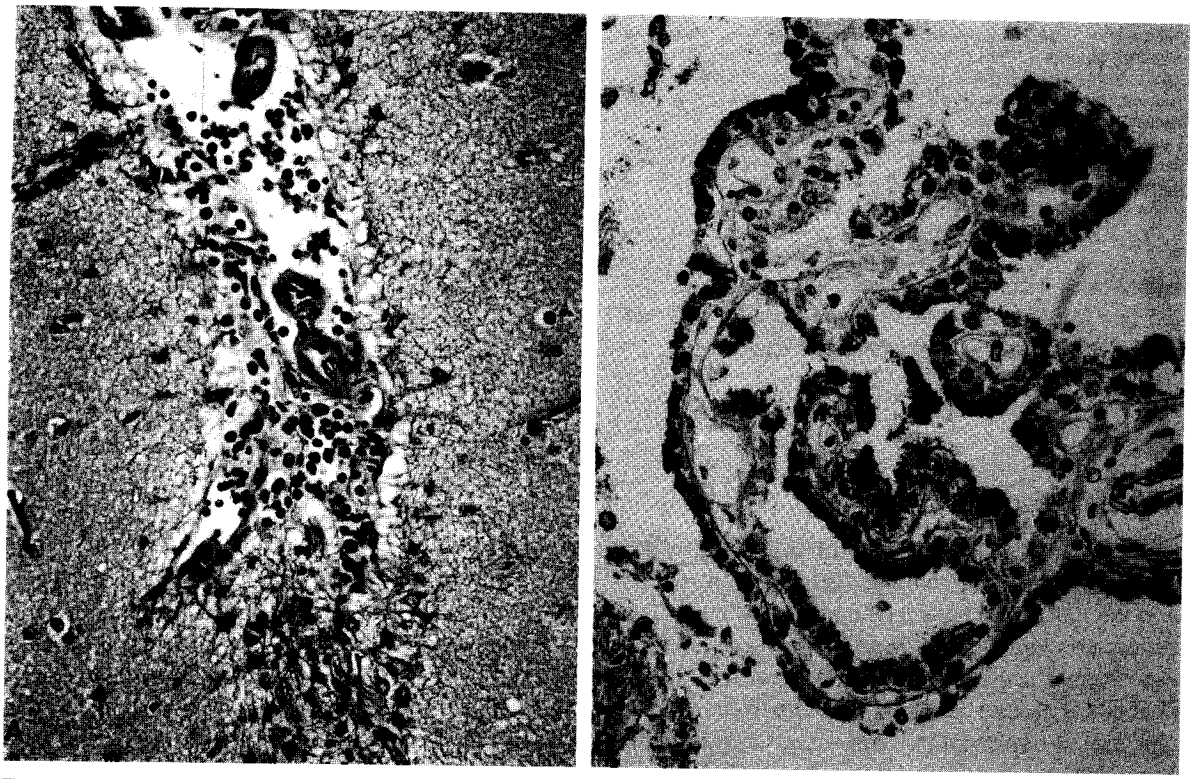

Figure 3. A: *Section of brain from a golden lion tamarin (FWZ) with naturally occurring callitrichid hepatitis showing lymphocytic infiltration of meninges (magnification, ×240; H&E).* B: *Choroid plexus from golden lion tamarin (HDZ) with lymphocytic meningitis similar to that depicted in* A, *showing abundant dark granular $LCMV_{CH}$ antigen within choroid cells. Magnification, ×300; immunoperoxidase stain.*

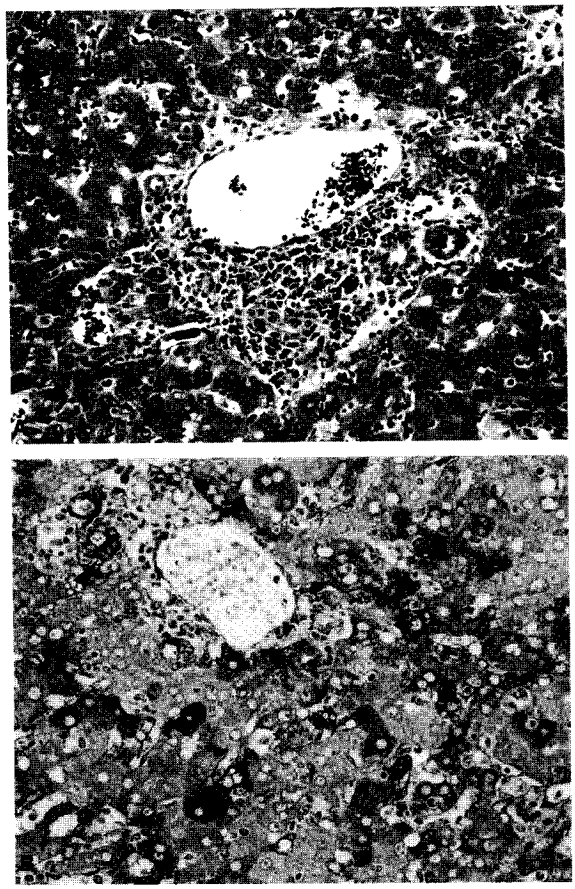

Figure 4. A: *Callitrichid hepatitis in a pygmy marmoset (HDZ) characterized by extensive lymphocytic triaditis; as contrasted with Figure 1A, hepatic plates are intact (magnification, ×200; H&E).* B: *Immunostain of the same $LCMV_{CH}$-infected pygmy marmoset liver depicted in* A, *with scattered cells containing $LCMV_{CH}$ product. Note antigen-positive biliary epithelium* (arrow) *in addition to the labeled hepatocytes (magnification, ×240; immunoperoxidase stain).*

sets, as well as focal colonic necrosis containing LCMV antigen. Lymphocytic pancreatitis was observed in two pygmy marmosets from which pancreas was available; viral antigen was particularly intense within areas of acinar degeneration in immunostained sections (Figure 5B). Unlike the common marmosets and tamarins, pygmy marmosets had clinical signs of respiratory distress and histological evidence of extensive interstitial pneumonia (Figure 6A). Antigen-containing alveolar macrophages were seen throughout the lungs and within bronchial lining cells. Furthermore, three of the five pygmy marmosets showed encephalitis with involvement of the neuropil and vasculitis (Figure 6B) more prominent than observed in the tamarins; however, viral antigen was not present in either the gray or white matter. In one pygmy marmoset, a small amount of viral antigen was detected in the meninges.

As in the tamarins, scattered glomeruli and segments of proximal convoluted tubules of two pygmy marmosets contained LCMV antigens despite the absence of any degenerative changes (Figure 7).

Discussion

Our pathological studies of both experimental and natural outbreaks of CH clearly establish the liver as a principal target for $LCMV_{CH}$ in all of the infected callitrichid primates. The FWZ tamarins and the experimentally infected common marmosets died 7 to 12 days after the onset of clinical signs with LCMV.[2,3] Hepatic necrosis was prominent and usually occurred with a slight lymphocytic response and no serological conversion in the fatal cases. LCMV antigens were predominantly observed in hepatic foci in various stages of degeneration and necrosis. As we previously reported, serum levels of liver transaminases and bilirubin were elevated during the acute phase of the disease.[2] Thus, in these common marmosets and tamarins, the primary mode of tissue injury in the liver was attributed to a direct cytopathic effect. Direct cell damage has also been attributed previously to mortality in common marmosets experimentally inoculated with Junin virus, the arenavirus that causes Argentine hemorrhagic fever in humans.[10,11]

In contrast, the pygmy marmosets experienced incubation periods that were 10 to 11 days longer than did the tamarins and common marmosets and died 16 to 24 days longer after infection.[2] These animals had prominent portal lymphocytic inflammation with little or no hepatic necrosis suggestive of an immune-mediated pathogenesis as opposed to the acute cytolytic process occurring in the common marmosets and tamarins.

The lymphocytic inflammatory changes noted in the meninges of the tamarins were mild compared with the gliosis and vasculitis seen within the neuropil of the pygmy marmosets. In fact, brain lesions in the pygmy marmosets were not unlike the more classic immunopathologically induced meningoencephalitis in adult mice inoculated intracerebrally with laboratory strains of LCMV.[12]

With the wide spectrum of extrahepatic lesions and the multi-organ distribution of LCMV antigens in the primates studied, it is clear that CH, like other arenavirus diseases of human and nonhuman primates,[8] is a widely disseminated systemic infection. It is particularly apparent that the histopathological changes associated with LCMV infection in the common marmosets and tamarins are, in part, analogous to the lesions reported for Lassa fever. For example, in human Lassa fever, the liver lesion is also charac-

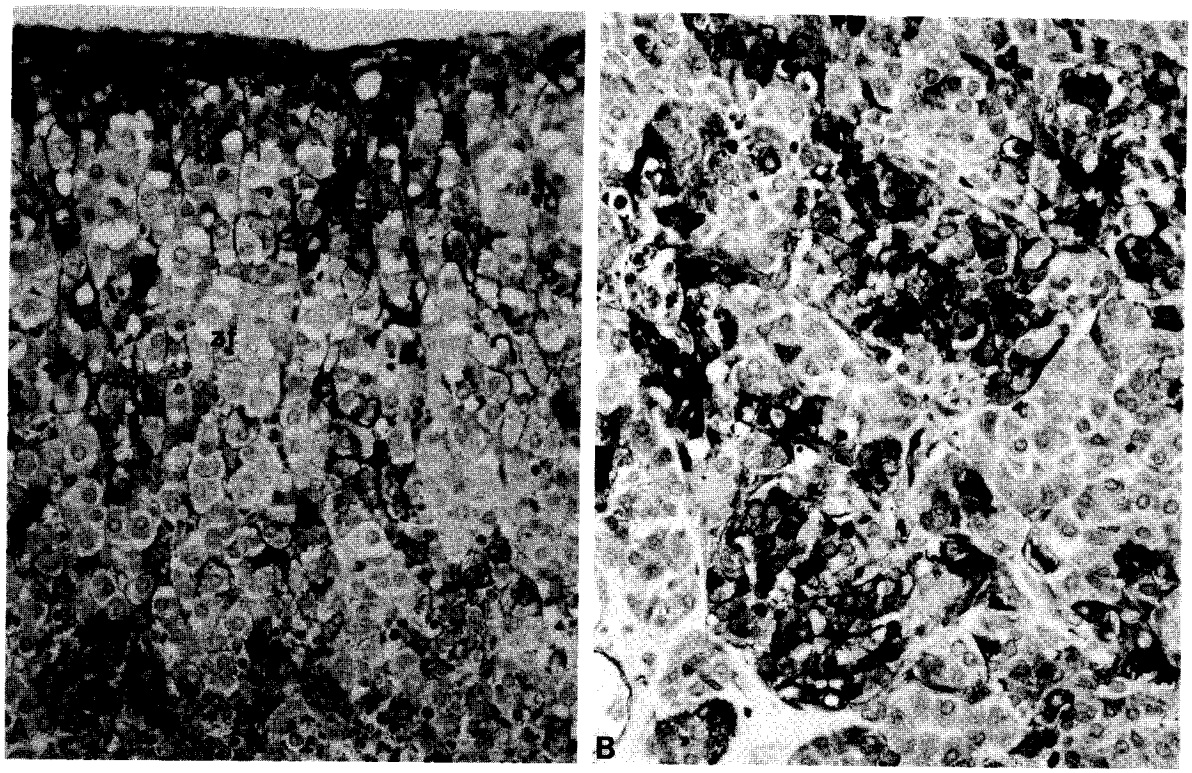

Figure 5. A: *Immunostain of $LCMV_{CH}$ antigen in adrenal gland and pancreas from pygmy marmoset from Figure 4A. Antigen-positive cortical cells in the zona glomerulosa* (top) *and the zona fasciculata (zf) are nondegenerate. Magnification, ×240; immunoperoxidase stain.* B: *Pancreatitis with clusters of $LCMV_{CH}$-containing acinar cells. Magnification, ×300; immunoperoxidase.*

terized by focal necrosis and Councilman-like bodies with a variable lymphocytic inflammatory response.[12] In addition to the present study, similar necrotizing hepatic lesions with Councilman-like bodies were described in earlier natural outbreaks of CH in *Callitrichidae*.[1] The necrosis in the spleen, abdominal lymph nodes, and adrenal cortex that we observed in many of the callitrichids is particularly reminiscent of Lassa fever infections in humans and experimental animals.[13–17] Furthermore, the widespread distribution of LCMV antigens in the liver, lung, spleen, pancreas, kidney, and adrenals of affected marmosets and tamarins parallels the antigen distribution in rhesus monkeys infected with Lassa fever virus as detected by immunofluorescence or immunohistochemistry (B. M. Connolly, unpublished data).

Arenaviruses bud from the plasma membrane of infected cells; therefore, our immunohistological findings support the premise that infectious virus can be shed via urine, feces, and oropharyngeal secretions as a consequence of virus budding in the mucosal lining cells of the bladder (Figure 2), intestine, and respiratory bronchioles. The transmission of $LCMV_{CH}$ between *Callitrichidae*, however, has not been documented via direct contact in any of the the CH outbreaks.

The specific mechanism of viral tissue tropism in these small South American primates remains unknown. One possibility is that variants of LCMV arising during persistent infections of the feed-mice or wild mice sources of primate infection may have an enhanced ability to replicate in a particular primate organ. In callitrichids, the liver appears to be the primary target of $LCMV_{CH}$ with the manifestation of a viral hepatitis. Multiple variants of LCMV have been isolated previously from persistently infected mice.[8,16–18] For these viruses, both the route of inoculation and the age of the murine recipient appear to be important determinants of the organ tropism, cytopathic effects, and persistence of the viral infection.[12,19]

To gain insight into the pathogenesis of arenavirus-induced human hemorrhagic fevers, arenaviruses of low virulence to humans have been adapted to different animal hosts to develop models for virulent infection. Pichinde virus, for example, is mild in humans but induces a disease in guinea pigs that is comparable to Lassa fever in humans and primates.[9,20,21] The pathological and immunohisto-

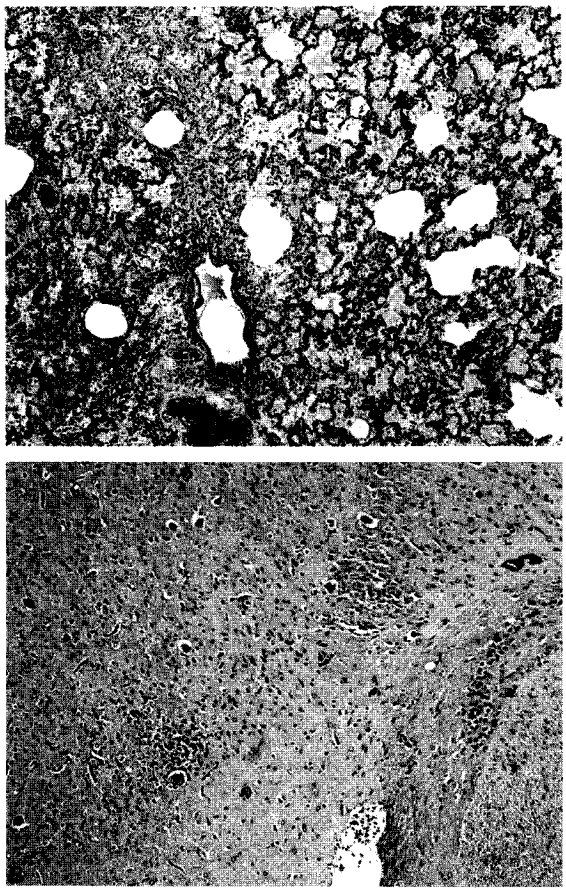

Figure 6. *Lung and brain from pygmy marmoset (FWZ) with proven CH shows extensive mononuclear interstitial pneumonia* (A) *(magnification, ×60; H&E) and encephalitis with glial foci and perivascular inflammation* (B) *(magnification, ×99; H&E), both attributed to* $LCMV_{CH}$ *infection.*

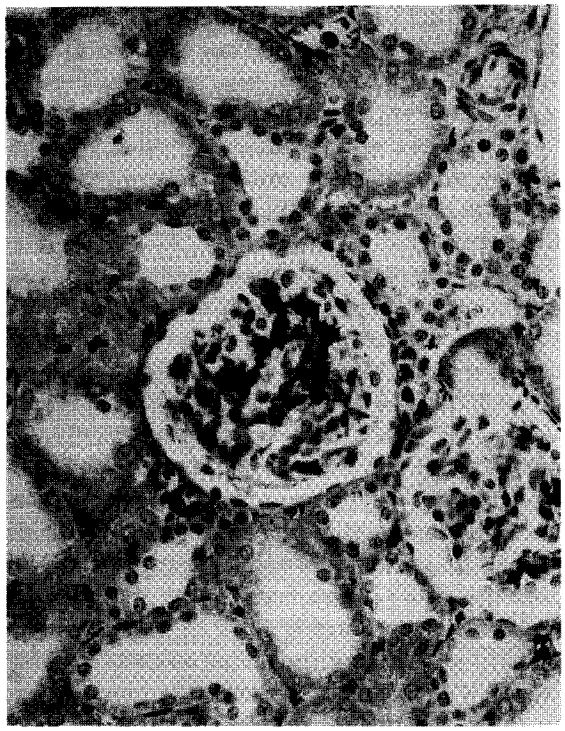

Figure 7. *Immunostain of kidney from pygmy marmoset (HDZ) from CH outbreak shows* $LCMV_{CH}$*-antigen-containing cells within glomerulus. Magnification, ×300; immunoperoxidase.*

chemical observations presented here for LCMV-induced CH in common marmosets and emperor and golden lion tamarins are similar to the lesions and antigen distribution of Pichinde virus infection in guinea pigs and Lassa fever virus infection in both guinea pigs and primates.[9,13,20,22] Thus, LCMV infections in the common marmoset may hold promise as another animal model for the hemorrhagic fevers caused by arenaviruses.

Of the several laboratory strains of LCMV known to induce infections in animal models, $LCMV_{WE}$ causes liver disease in macaques and guinea pigs.[8] In humans, LCMV is a rodent-borne disease usually associated with a flu-type illness. LCMV has a predilection for the central nervous system that often results in aseptic meningitis and, rarely, fatal encephalitis. Recent human serosurveys continue to support earlier studies showing a prevalence of 6 to 10% of LCMV infection in certain populations in the the U.S.[5,23,24] Futhermore, in mouse colonies, LCMV can be spread by transplantation of animal tumors,[19,25] a mechanism that may increase the potential hazard of this virus in the human transplantation recipients.[5]

In depth pathological studies of the few fatal cases of human LCMV available suggest that host-mediated immunopathological mechanisms play an important role; however, the precise pathogenesis and limits of the organotropism of LCMV in man remains unknown.[12] In our primate studies, different species susceptibilities to LCMV were recognized; experimentally and naturally infected common marmosets and tamarins died with acute liver cell damage usually before antibody response to LCMV was detectable,[24] whereas the more prolonged course of the disease with lymphocytic infiltrates in pygmy marmosets suggested an immune-cell-mediated pathogenesis as reported in mice and postulated for humans. It is also possible that novel LCMV strains have emerged as hepatotropic strains in marmosets and tamarins that could behave similarly in humans. Although overt human disease caused by $LCMV_{CH}$ has not been documented, seroconversion has occurred in several caretakers involved in CH outbreaks.[2] It would be prudent to investigate LCMV as a possible causative factor in those sporadic cases of human hepatitis that cannot be attributed to any of the known human hepatitis viruses.

In a seroepidemiological investigation for antibodies to LCMV in zoo-exhibited primates and primate research centers and at a reserve for endangered tamarins in Brazil, approximately 5% of New and Old World monkeys were seropositive.[24] All LCMV-seropositive primates were among those exhibited in zoos and almost all were found in sites with reported CH outbreaks.

Arena- and other rodent-borne hemorrhagic fever viruses are gaining increasing global significance as important causes of emerging human virus diseases. Excellent examples of these include outbreaks of the new hemorrhagic fever caused by Guanarito virus in Venezuela[26,27] and episodes of human Hantavirus pulmonary infections that occurred recently in Southwestern U.S.[28] The pathological and immunohistochemical observations reported here in our study indicate that marmosets and tamarins, whether experimentally or naturally infected with LCMV, exhibit a disease process that is closer to arenaviral hemorrhagic fevers than to the typical neurotropic LCMV infections known to occur in man. The common marmosets experimentally infected with $LCMV_{CH}$ appear to follow the same disease course as the naturally infected callitrichids. Additional studies in marmosets to elucidate the pathogenesis of this emerging disease may be beneficial to both humans and endangered primates at risk for LCMV.

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