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Liver Disease in Rhesus Monkeys Infected with Simian Immunodeficiency Virus

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Rhesus monkeys infected with simian immunodeficiency virus (SIV) develop a syndrome very similar to patients with acquired immune deficiency (AIDS), including liver disease. This prospective study was undertaken to define the pathology, course, and pathogenesis of liver disease in 20 rhesus monkeys (Macaca mulatta) ***after intravenous inoculation with the standardized isolate SIV/DeltaB670. Tissue samples from liver and gallbladder between 2 and 24 weeks after inoculation were examined histologically and immunohistochemically for SIV gag protein p26, and by*** in situ ***hybridization with an SIV riboprobe. Histologically there was infiltration of portal tracts and around hepatic veins and venules by mononuclear inflammatory cells, focal bile duct damage, proliferation of bile ductules, and focal lobular inflammation as early as 2 weeks after infection. The severity and extent of these lesions were graded semiquantitatively and showed that bile duct damage and hepatic venulitis were the most significant changes. Simian immunodeficiency virus gag protein p26 and SIV RNA were detected in scattered mononuclear cells in portal tracts and sinusoids, but not in hepatocytes or bile duct epithelial cells. The data indicate that the liver is involved early during the course of SIV infection, followed by persistent changes until the terminal stage of the disease. Our findings suggest that the liver damage in SIV-infected rhesus monkeys is similar to the changes observed previously in AIDS patients. (Am J Pathol 1991, 139:1081–1088)***

Infections with human or simian immunodeficiency viruses (HIV or SIV) cause acquired immune deficiency syndrome (AIDS) in humans and in rhesus monkeys. The manifestations of HIV infections are both primary, ie, due directly to the cytopathic effect on T-helper lymphocytes, and secondary, due to impairment of cell-mediated immunity, autoimmune phenomena, opportunistic infections, or malignant tumors.[1] The immune defect in AIDS has been well documented, but the pathogenesis of tissue injury remains unclear. This question can be investigated in rhesus monkeys after infection with SIV. This lentivirus is morphologically, antigenically, genetically, and biologically closely related to HIV.[2,3] After inoculation into susceptible macaques, SIV causes an immunodeficiency disease that closely resembles human AIDS and therefore represents an excellent animal model for this syndrome.[4–9]

A wide spectrum of liver diseases has been reported in patients with AIDS-related complex (ARC) or AIDS. These include acute and chronic hepatitis, granulomas, neoplasms, vascular lesions, biliary tract diseases, and miscellaneous lesions.[10–15] Preliminary studies of the liver of macaques with SIV infection showed alterations similar to those observed in the livers of AIDS patients. Baskin et al[6] described hepatic lesions characterized by infiltration of portal tracts by mononuclear inflammatory cells and mild proliferation of intrahepatic bile ductules in 8 of 18 SIV-infected monkeys examined at necropsy. The biliary tract lesions were associated with cytomegalovirus (CMV) and with cryptosporidium infection in two cases each[16,17] and have been described in detail.[7,16] To date there has been no report of primary or specific hepatic lesions in AIDS. The aim of this prospective study was to define the pathology, course, and pathogenesis of liver disease in macaques after inoculation with SIV.

Material and Methods

Animals

Twenty-four rhesus monkeys *(Macaca mulatta)* were used in this experiment. They were born into the outdoor

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breeding colony of the Tulane Regional Primate Research Center (TRPRC), which has been shown to be free of naturally occurring SIV and type D retroviruses. The monkeys were removed from their mothers within 3 days of birth and raised in the nursery before inoculation. This prevented natural infection with opportunistic agents such as CMV and Rh-EBV (Epstein–Barr virus), which could complicate the results of the study. The monkeys were individually caged in an indoor isolation facility, fed a standard laboratory diet, and given water *ad libitum* as soon as they were removed from the nursery.

Inoculations

Simian immune deficiency virus/DeltaB670 originated from a spontaneously infected sooty mangabey monkey *(Cercocebus atys)*[4,6] and was isolated from a lymph node of an experimentally infected rhesus monkey. This isolate was subsequently propagated in culture and numerous aliquots were cryopreserved for use as a standardized inoculum. This inoculum contains 10,000 monkey ID50 per milliliter and consistently results in 100% infection of rhesus monkeys. Approximately 70% of infected monkeys die of immunodeficiency disease within 7 months of inoculation (reference 18; also unpublished observations). For this study, 20 monkeys were inoculated intravenously at 8 months of age with 1 ml undiluted cryopreserved standardized inoculum of SIV/DeltaB670. The remaining four monkeys were inoculated with supernatant from uninfected cultured cells, thus serving as uninfected controls.

Serial Killing

Four monkeys each were killed at the following time points: 2, 4, 8, and 24 weeks after inoculation. The remaining 4 animals were killed when moribund (at 9, 11, 19, and 21 weeks) to examine animals in the terminal stage of the disease. These intervals were chosen to be able to examine tissues both in the very early stages of infection, sequentially as immunologic dysfunction and liver disease developed, and in the terminal stage of disease. Two of the controls were killed after 12 weeks, and the remaining two after 24 weeks.

Light Microscopy

All monkeys received a complete necropsy examination at TRPRC. Four tissue samples from the liver (one from each lobe, one sample from the hepatic hilus, and one from the liver with intrahepatic gallbladder) were obtained at the time of necropsy. The specimens were fixed in 10% buffered formaldehyde, embedded in paraffin, and stained with hematoxylin and eosin (H&E) and periodic acid-Schiff after diastase digestion (D/PAS). Sections were examined in a blinded fashion by two investigators. The following morphologic changes were evaluated: inflammation of portal tracts, bile duct damage, proliferation of bile ductules, inflammation of lobular parenchyma, focal necrosis of hepatocytes, endothelitis, inflammation of hepatic veins and venules, hyperplasia of Kupffer cells, presence of multinucleated giant cells, and other alterations. The severity of these lesions was graded semiquantitatively as absent (0), mild (+), moderate (+ +), or severe (+ + +), and the extent of the portal tract abnormalities was quantitated in 10 portal tracts of each case.

Immunohistochemical Analysis

Forty-eight liver and gallbladder sections (obtained from two different blocks of each case) were stained with mouse monoclonal antibody to SIV gag protein p26. A modified immunocytochemical avidin-biotin peroxidase complex (ABC) method was used as described previously.[19,20] Briefly, deparaffinized and rehydrated sections were incubated with 3% hydrogen peroxide in 1% methanol for 30 minutes to block endogenous peroxidase. The slides were washed for 10 minutes in phosphate-buffered saline (PBS) (pH 7.4) and incubated with 3% normal horse serum for 30 minutes. Then the slides were drained and the optimal dilution (1:100) of the antibody to p26, as determined in our laboratory on SIV-positive tissue sections, was applied overnight at room temperature in a humid chamber. After this, the slides were incubated with biotinylated, affinity-purified horse anti-mouse antibody diluted 1:200 (Vector Laboratories, Inc., Burlingame, CA). After a 10-minute wash in PBS, the sections were incubated for 30 minutes with ABC (1:500) followed by 3,3′-diaminobenzidine tetrachloride, containing 0.03% (vol/vol) hydrogen peroxide as a chromogen substrate for 7 minutes. Then the slides were rinsed in PBS for 2 minutes and counterstained with hematoxylin. As controls, normal mouse serum or PBS instead of the monoclonal antibody were used. Sections of lung of an SIV-infected monkey with numerous p26-positive giant cells were used as positive control.

In Situ *Hybridization*

For *in situ* hybridization,[21] tissues were placed on ornithine-carbamoyltransferase (OCT) medium, snap frozen in liquid nitrogen, and stored at −70°C. Tissues were sectioned on a cryostat, placed on coated slides, and

immersed in 4% paraformaldehyde in phosphate-buffered saline for 20 minutes. Fixed sections then were washed three times in buffer, dehydrated in ethanol, and air dried.

The S^{35}-labeled RNA probe was prepared from a positive SIV DeltaD915 lambda clone, digested with various restriction endonucleases, and size fractionated by agarose gel electrophoresis. Restriction fragments were transferred onto nitrocellulose filters by Southern blot and probed with P^{32}-labeled pK2BA representing the 7.5-Kb internal region of SIV_{agm} provided by J. Mullins. The 4-Kb SIV DeltaD915 fragment was electroeluted from the gel and subcloned into plasmid pGEM 3Z at *Sma* I and *Sst* I sites (designated pHU 101). The pHU 101 was further digested with restriction endonuclease *Sal* I, which cuts at the *Sal* I site in the viral genome and the plasmid. The *Sal* I digested pHU 101 was allowed to ligate so that the 3.2-Kb SIV DeltaD915 insert was free from cellular and human repetitive sequences (designated pHU 102). The pHU 102 DNA was linearized at either the *Sst* I or *Sal* I site and was transcribed for the antisense and sense strand RNA. The transcription mixture included 24 µmol/l (micromolar) S^{35} UTP 1000 Ci/mmol (NEN), 40 mmol/l TRIS-HCl, pH 7.5, 10 mmol/l Tricine, 6 mmol/l $MgCl_2$, 2 mmol/l spermidine, 10 mmol/l NaCl, 10 mmol/l dithiothreitol (DTT), 0.5 mmol/l each of adenosine triphosphate, cytidine triphosphate, and guanosine triphosphate, 0.2 mg/ml linearized template DNA (pHU 102), 1.6 U/µl RNasin ribonuclease inhibitor, and 20 U/µl T7 or SP6 polymerase. The reaction mixture was incubated at 37°C for 1 hour, and the S^{35}-labeled RNA was purified by Sephadex G-50 column chromatography and ethanol precipitated. Usually >80% of S^{35} uridine triphosphate (UTP) was incorporated. Purified RNA was stored at −70°C until used.

Fixed slides were rinsed briefly in 2× standard saline citrate (SSC; 0.3 mol/l NaCl/0.03 mol/l sodium citrate), treated with 0.5 mg/ml proteinase K for 10 minutes at 37°C, acetylated in acetic anhydride/triethanolamine, pH 8.0, rinsed briefly in 2× SSC, and immersed in 0.1 mol/l TRIS-HCl, pH 7.0, with 0.1 mol/l glycine for 30 minutes. Slides then were rinsed in 2× SSC and dehydrated in ethanol. The hybridization mixture contained S^{35}-labeled RNA probe, 50% formamide, 2× SSC, 10 mmol/l DTT, 10% dextran sulfate, 1× Denhardt's solution, 20 mmol/l TRIS, pH 8.0, 5 mmol/l ethylenediaminetetra-acetic acid, pH 8.0, and 500 µg/ml yeast RNA. Twenty microliters of hybridization mixture containing 1.5 × 10^6 cpm S^{35}-labeled probe was applied to each slide, covered with a precleaned coverslip, and sealed with rubber cement. Hybridization was carried out in a moisture chamber at 37°C overnight. Slides were rinsed thoroughly with 4× SSC to loosen the coverslip and remove the bulk of the hybridization mixture. Ribonuclease treatment with RNase A (100 µg/ml), and RNase T_1 (1 µg/ml) was carried out for 30 minutes at 37°C. Slides then were incubated in 50% formamide, 2× SSC, 10 mmol/l DTT at 52°C overnight. Slides were washed in 2× SSC at 52°C, 0.1× SSC at 45°C and dehydrated in ethanol. Hybridized preparations were autoradiographed with Kodak NTB 2 nuclear track emulsion diluted 1:3 in 300 mmol/l ammonium acetate. After exposure for 2 to 7 days at 4°C, slides were developed with D-19 at 15°C, air dried, and stained with hematoxylin and eosin. For all specimens, tissue sections also were hybridized with a control probe, which was transcribed from the sense strand of SIV DeltaD915 in pHU 102. Infected positive control tissues (lymph nodes) and uninfected negative control tissues were hybridized in parallel during each run.

Statistical Analysis

Differences in number of abnormal portal areas (portal inflammation, bile duct damage, or proliferation of bile ductules) in animals killed at 2, 4, 8 to 11, and 19 to 24 weeks of age and control animals were tested using analysis of variance. Severity of lesions (intralobular or perivenular inflammation) were rated as described above (− = 0, + = 1, ++ = 2, +++ = 3), and were tested similarly for differences between groups.

Results

All of the inoculated monkeys became infected with SIV as determined by reisolation of virus in culture and the presence of viral antigen in serum (data not shown). Four of the monkeys became moribund with diarrhea and wasting and were killed at 9, 11, 19, and 21 weeks, respectively, after inoculation. The other animals showed clinical signs of lymphadenopathy, rash, and intermittent diarrhea, but did not become seriously ill before scheduled killing. None of the monkeys had symptoms related to liver disease, and laboratory studies showed no consistent alterations in serum proteins or aminotransferase activities.

Histologically the liver tissue of SIV-infected monkeys showed varying degrees of bile duct damage and proliferation of bile ductules as well as portal, intralobular, and perivenular inflammation. The results of the semiquantitative evaluation of these morphologic changes by two investigators were comparable, and there were no major differences between the three liver samples obtained from each monkey. The extent of the lesions varied significantly between monkeys killed at the same time point, however, and therefore were averaged as shown in Table 1.

Table 1. *Histologic, Immunohistochemical and* In Situ *Hybridization Findings in Livers of SIV-Infected Rhesus Monkeys*

Weeks postinoculation	Portal inflammation	Damage of bile ducts	Proliferation of bile ductules	Intralobular inflammation	Perivenular inflammation	SIV gag protein p26	SIV RNA
2 weeks (4 monkeys)	97.5*	55*	67.5*	4/4†	4/4†	0/4†	2/4†
4 weeks (4 monkeys)	32.5	67.5	75	2/4	4/4	1/4	0/4
8–11 weeks (6 monkeys)	33	57	52	4/6	6/6	2/6	0/6
19–24 weeks (6 monkeys)	58	75	78	5/6	6/6	4/6	3/6
Uninfected controls (4 monkeys)	27.5	40	17.5	1/4	1/4	0/4	0/4

* Percentage of 40–60 portal tracts (10 for each case) with abnormality.
† Number of cases with abnormality/total number of cases in group.

The portal tracts were infiltrated by mononuclear inflammatory cells composed mainly of lymphocytes with a few plasma cells, histiocytes, and occasional eosinophils (Figure 1). Multinucleated giant cells were present in the portal tracts in two cases. The extent of portal inflammation varied moderately among the monkeys and was most widespread 2 and 24 weeks after SIV infection, as summarized in Table 1. In the control group, two cases showed a small number of portal tracts with mild to moderate, mainly mononuclear cell infiltration. In one control case, hematopoietic cells were predominant.

Bile duct damage was mild and was characterized by focal degeneration and hyperplasia of epithelial cells, infiltration by few lymphocytes, and slight disruption of the basement membrane, as seen on D/PAS stains (Figure 2). These changes involved small and medium-sized bile ducts. Conspicuous proliferation of bile ductules was present in many monkeys. Control monkeys did not show any evidence of bile duct damage and only focal proliferation of bile ductules.

Lobular inflammation was present to variable degrees in the majority of the infected monkeys and was most extensive at 2 and 24 weeks after inoculation. It was characterized by infiltration of sinusoids by inflammatory cells, predominantly lymphocytes. Hyperplasia of Kupffer cells was always found and in two cases was accompanied by features of erythrophagocytosis. Scattered focal necroses of hepatocytes with occasional formation of acidophilic bodies was seen in all cases. In addition, hepatocytes showed slight degenerative changes, such as focal cytoplasmic swelling.

Perivenular inflammation was present in all SIV-infected monkeys and one control monkey. The infiltrate was composed of mononuclear inflammatory cells, mainly lymphocytes, macrophages, and few plasma cells. The inflammatory cells either formed nodular aggregates resembling lymphoid follicles (Figure 3) or diffusely infiltrated the wall and intima of hepatic veins, the latter primarily at 2 weeks. The vascular lumina were patent, but lymphocytes adhered focally to the endothelium (Figure 4). In three cases, multinucleated giant cells were detected within the perivenular infiltrate. Occasional foci

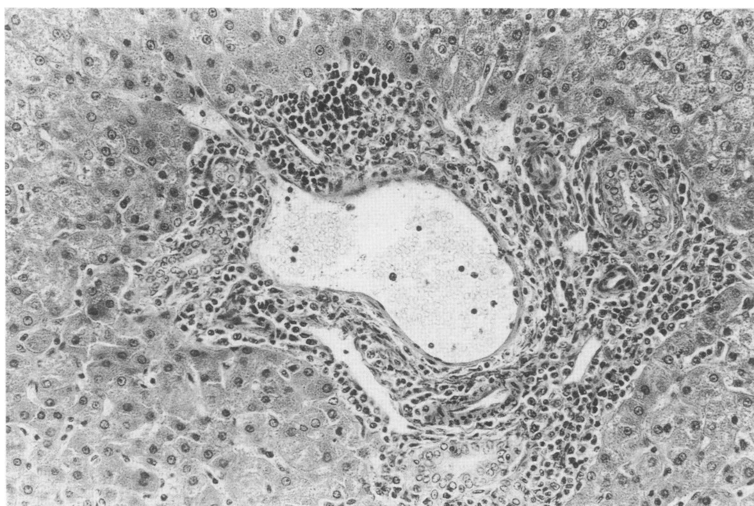

Figure 1. *Portal tract of SIV infected monkey showing diffuse infiltration by mononuclear cells. Proliferation of bile ductules is also seen, H&E, ×250.*

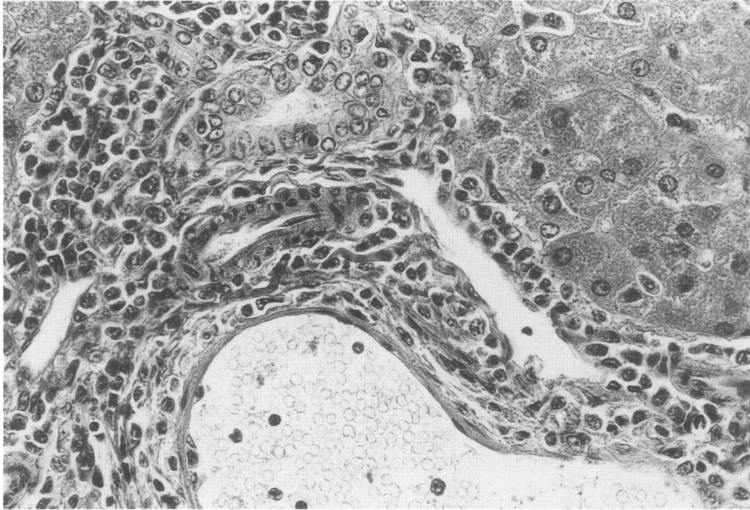

Figure 2. *Higher magnification of portal tract shown in Figure 1. The bile duct epithelium is infiltrated by lymphocytes (arrows), H&E, ×400.*

of hematopoiesis were seen in sinusoids and in portal tracts in four cases. The control livers did not show any significant necroinflammatory lesions in the lobular parenchyma.

Statistical evaluation of these histologic changes showed significant differences between the five groups of monkeys (2, 4, 8 to 11, 19 to 24 weeks, and controls) for portal inflammation ($P = 0.037$), for bile duct damage ($P = 0.004$), and for perivenular inflammation ($P = 0.0002$). Scheffe *post hoc* tests indicated significant differences between controls and animals killed 4 and 19 to 24 weeks after inoculation for bile duct damage and between controls and animals sacrificed 2, 8 to 11, and 19 to 24 weeks after inoculation for perivenular inflammation.

Infection of large intrahepatic bile ducts and gallbladder with cryptosporidium was observed in two cases. The cryptosporidial organisms invaded the apical aspects of the epithelial cells surrounded by polymorphonuclear leukocytes. There also was glandular hyperplasia and inflammatory infiltration with follicle formation in the wall of the gallbladder in SIV-infected and control monkeys. The common bile ducts were examined grossly at necropsy and were patent.

Simian immune deficiency virus gag protein p26 was expressed in the cytoplasm of very few mononuclear cells in portal tracts and sinusoids of SIV-infected monkeys, but not in giant cells, hepatocytes, or bile duct epithelial cells. Morphologically the positive cells resembled lymphocytes and macrophages (Figure 5). The number of cases demonstrating p26 expression increased with time after inoculation (Table 1). By *in situ* hybridization, SIV RNA was detected in scattered mononuclear cells in portal tracts and perivenular inflammatory infiltrates at 2 and 19 to 24 weeks after inoculation (Figure 6). The uninfected control monkeys and control slides did not show any detectable immunostaining or hybridization signals,

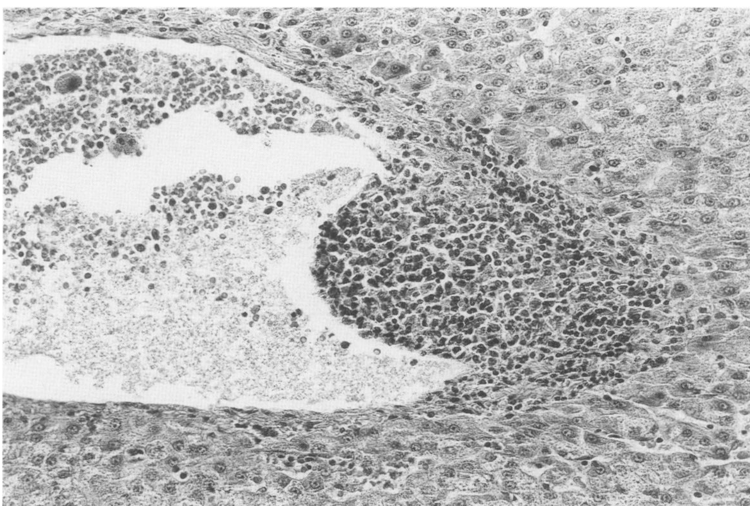

Figure 3. *Nodular aggregate of mononuclear inflammatory cells in wall of sublobular hepatic vein of SIV infected monkey, H&E, ×250.*

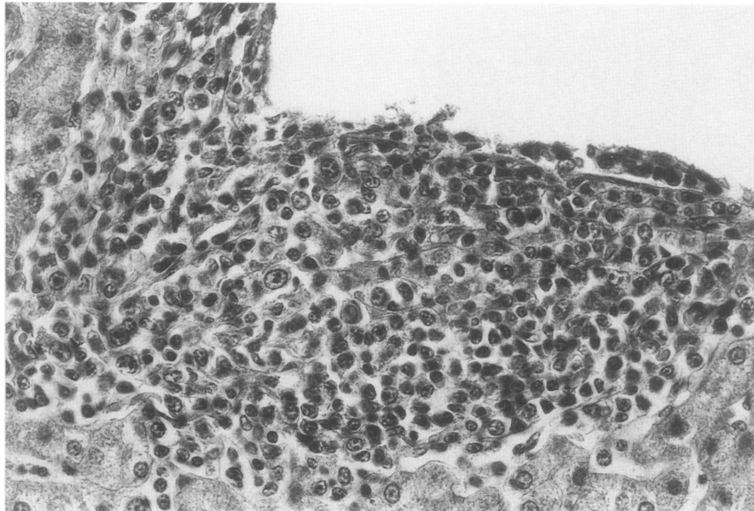

Figure 4. *The wall including the endothelial cells of hepatic vein of SIV infected monkey are diffusely infiltrated by mononuclear cells. H&E, ×400.*

whereas the SIV-positive control slides exhibited strong staining and hybridization reactions.

Discussion

Almost all patients with ARC or AIDS have asymptomatic hepatomegaly or abnormal biochemical findings, particularly elevation of alkaline phosphatase and aminotransferase activities.[10–15] Histologically the liver is abnormal in more than 90% of patients with AIDS and therefore represents a common site of involvement in this syndrome. The manifestations in the liver are diverse, however, and often are secondary to complications of acquired immunodeficiency such as infections or neoplasms. To date, no findings specific or pathognomonic for AIDS have been identified in the liver by light microscopy. Recently several groups of investigators, including our group, reported necroinflammatory lesions of the bile ducts and proliferation of bile ductules in AIDS patients.[13,21] We have observed similar changes in the livers of rhesus monkeys with SIV infection. The cause of bile ductule proliferation is not known, but it may be related to bile duct damage. Inflammatory infiltration of portal tracts showed two peaks at 2 and 19 to 24 weeks after inoculation, in parallel with the detection of SIV RNA in mononuclear cells by *in situ* hybridization. The expression of SIV gag protein p26 in mononuclear cells increased slowly during the experimental period and reached a maximum at 19 to 24 weeks after inoculation. The most conspicuous hepatic lesions in the livers of SIV-infected macaques were bile duct damage and dense lymphocytic infiltration of terminal hepatic venules and sublobular hepatic veins. The venulitis was far more extensive than the mild endothelitis of terminal hepatic venules and portal veins in some children with AIDS.[22] In the monkeys, the venulitis appeared early (2 weeks) after

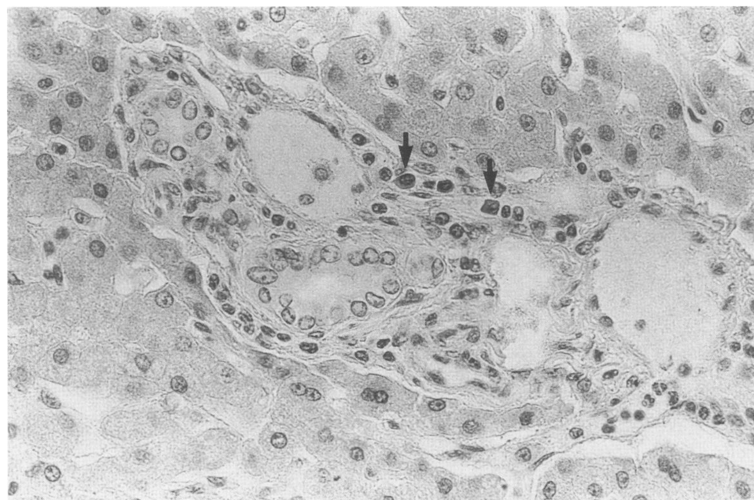

Figure 5. *Several lymphoid cells (arrows) in the portal tract of an SIV infected monkey show staining of the cytoplasm by monoclonal antibody to SIV gag protein p26, ABC method, ×400.*

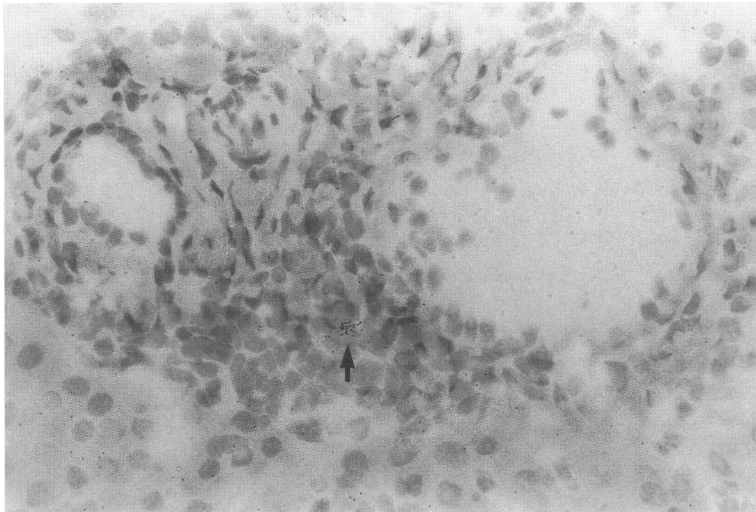

Figure 6. *One lymphoid cell (arrow) in portal tract of SIV infected monkey shows hybridization signal indicating the presence of SIV RNA,* In situ *hybridization,* ×*400.*

SIV infection, together with other inflammatory changes in the liver and viral RNA, and persisted until the terminal stage of the disease.

The pathogenesis of liver injury in patients with AIDS and in SIV-infected macaques is unknown. Several possibilities should be considered. First HIV or SIV may infect bile duct epithelial cells or hepatocytes and the virus or its proteins may be directly cytotoxic to these cells. We did not find SIV antigen or SIV RNA in liver epithelial cells, but this possibility cannot be ruled out until more sensitive detection methods are employed. Recently several hepatoma cell lines have been demonstrated to support productive infection by HIV.[23] Clearly the cell types that are susceptible to HIV or SIV infection are more diverse than initially reported and may include epithelial cells.[24–29] Second immunologic mechanisms may be involved in liver damage. The degenerative and inflammatory lesions of small bile ducts and of hepatic veins and venules resemble the alterations seen in the liver in graft-*versus*-host disease or in hepatic allograft rejection.[30] It has been hypothesized that the cutaneous exanthem in SIV-infected rhesus monkeys and apoptosis of epithelial cells in rectal and colonic mucosa in many AIDS patients are similar to acute allograft rejection or acute graft-*versus*-host disease.[31,32] These similarities are supported by our recent observation that the damaged bile duct epithelial cells in AIDS patients showed induction of HLA class II antigens,[33] as is seen also in patients with graft-*versus*-host disease or hepatic allograft rejection. Although the biologic and immunologic significance of HLA class II antigen expression on bile duct epithelial cells in patients with AIDS is not clear, it does not appear to be a nonspecific reaction to all types of liver injury, as indicated by our previous studies.[19] It is possible that either HIV/SIV genes or lymphokines such as interferon or tumor necrosis factor released from infected macrophages[34] may induce HLA expression in bile ducts and endothelial cells and may trigger an immunologic response leading to damage of these structures.

Rhesus monkeys infected with simian immune deficiency virus are currently the best available animal model with which to study lentivirus-induced immunodeficiency disease.[9] Despite some differences, this experimental model provides the opportunity to investigate both the primary and secondary changes and to gain insight into the pathogenesis of the hepatic lesions. In addition, the SIV-infected macaques represent an ideal model for studies of antiviral drug testing, immunotherapy, and vaccination.

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