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Peliosis Hepatis and Sinusoidal Dilatation During Infection by the Human Immunodeficiency Virus (HIV)

An Ultrastructural Study

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The description of hepatic sinusoidal lesions in a significant number of acquired immunodeficiency syndrome (AIDS) patients prompted the authors to undertake an ultrastructural study of the sinusoidal barrier abnormalities during human immunodeficiency virus (HIV) infection, in order to compare these lesions with those described in other conditions and to discuss their possible origin. In a series of 29 patients with serologic evidence of HIV infection and liver abnormalities, 8 (28%) had sinusoidal lesions. Peliosis hepatis was present in 2 cases, and sinusoidal dilatation in 6. These patients were classified as follows: 3 AIDS, 4 AIDS-related complex, 1 unclassifiable. Ultrastructural lesions of the sinusoidal barrier were observed in all the cases. They closely mimicked the changes previously reported in peliotic and peliotic-like changes of various origins. A striking particularity was, however, the presence of numerous and hyperplastic sinusoidal macrophages. This work suggests that an injury of the endothelial cells, directly or indirectly related to the presence of HIV, may be incriminated in the pathogenesis of sinusoidal lesions during HIV infection. (Am J Pathol 1988, 131:38–47)

A VARIETY of histologic abnormalities has been described in the liver during the acquired immunodeficiency syndrome (AIDS). Most of these lesions are the consequence of liver involvement by disseminated opportunistic infections or by malignancies, including Kaposi's sarcoma and non-Hodgkin's lymphomas.[1–6] An unexpected finding is the occurrence of sinusoidal abnormalities in a significant number of cases.[7–11] These abnormalities range from sinusoidal dilatation[7,8,9] to typical peliosis hepatis.[8,10,11] The purpose of this work was to perform an ultrastructural investigation of sinusoidal barrier abnormalities in a series of patients with serological evidence of human immunodeficiency virus (HIV) infection, in order 1) to compare these lesions with those described in the other conditions associated with the occurrence of sinusoidal lesions and 2) to discuss their possible origin.

Materials and Methods

Selection of Patients

A total of 29 patients was studied. All these patients had serologic evidence of HIV infection. Anti-HIV antibodies were detected by an HIV enzyme immunoassay, and seropositivity was confirmed by a Western

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Table 1—Relevant Clinical and Laboratory Data at the Time of Liver Biopsy for The Patients Included in the Study Group

Cases	Liver morphology	Age/Sex	Clinical diagnosis	Risk factor	Liver tests					Viral status	Intercurrent general (G) and liver (L) pathology
					Bil	AP	ASAT	ALAT	GGT		
1	Sin dilat	41/M	AIDS	Homosexual	N	2N	N	N	2N	HBc^+	G: Kaposi's sarcoma L: Granulomas
2	Sin dilat	54/M	AIDS	Homosexual	N	3N	N	N	N	HBs^+	G: Mycobacteriosis Candidiasis CMV colitis L: Granulomas
3	Sin dilat	47/F	AIDS	Blood transfusion	2N	14N	3N	2N	61N	HBs^-	G: Pneumocystis Cryptosporidiosis L: Chronic hepatitis
4	Sin dilat	31/M	ARC	Drug addict	N	N	2N	2N	2N	HBs^-	None
5	Sin dilat	21/M	ARC	Drug addict	N	N	N	3N	2N	HBs^+	None
6	Sin dilat	23/M	ARC	Homosexual drug addict	N	N	N	2N	N	HBs^+	None
7	Peliosis	41/M	ARC	Homosexual	N	N	2N	N	N	HBs^+	G: None L: Chronic hepatitis
8	Peliosis	27/M	NC	Drug addict, Carribbean	N	N	N	N	3N	HBs^+	G: Myeloid disorder L: Myeloid metaplasia

Sin dilat, sinusoidal dilatation; M, male; F, female; NC, unclassifiable; Bil, bilirubin; AP, alkaline phosphatase; ASAT, aspartate aminotransferase; ALAT, alanine aminotransferase; GGT, -glutamyl transpeptidase; N, normal value; CMV, cytomegalovirus.

blot test. All the patients underwent a percutaneous liver biopsy for diagnostic purposes, because of clinical or biologic manifestations suggestive of hepatic dysfunction. According to the criteria of the Centers for Disease Control,[12] the clinical diagnosis was acquired immunodeficiency syndrome (AIDS) in 19 cases and AIDS-related complex (ARC) in 5 others. Four patients were considered asymptomatic carriers. The last patient was unclassifiable according to the above criteria; his clinical presentation is detailed below. For each of the 29 patients, in addition to conventional histologic processing, a portion of the liver tissue was prepared for an electron-microscopic examination according to the techniques described below. An examination of the semithin sections was performed in all cases. Sinusoidal lesions were observed in 8 cases, which were retained for an ultrastructural examination. The other cases, in which no sinusoidal lesion was noted, were not further investigated. The relevant clinical and laboratory data for the 8 patients included in the study group are listed in Table 1. The condition of 3 patients (Cases 1–3) was classified as AIDS, and that of 4 others (Cases 4–7) as ARC. Patient 8 was not classifiable according to the usual criteria. He was not affected by any opportunistic infection or by any of the malignancies usually associated with AIDS. HIV infection was diagnosed during the evaluation of an acute myeloid disorder with myelofibrosis and extramedullary hematopoiesis. The hematologic presentation of this patient has been detailed in a previous report.[13] Neither patient received any of the drugs known to be associated with the occurrence of peliosis hepatis.[14]

Tissue Processing

A portion of the liver biopsy was processed according to conventional histologic techniques. Sections were stained with hematoxylin and eosin (H & E), Masson's trichrome, the Gordon–Sweet method for demonstration of reticulin fibers, and, when appropriate, special histochemical techniques, including Grocott methenamine silver and Ziehl–Neelsen acid fast. Another portion of the liver biopsy was cut into 1-cu mm blocks, immediately fixed into 2.5% phosphate-buffered glutaraldehyde, pH 7.4, for 2 hours, and rinsed in phosphate buffer. The blocks were postfixed in veronal-buffered 1% osmium tetroxide, pH 7.2, dehydrated through graded alcohols and propylene oxide, and embedded in epoxy resin. One-micron-thick sections were stained with toluidine blue and examined with a light microscope. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with an electron microscope (Siemens Elmiskop IA).

Results

Light-Microscopic Findings

In Cases 1–6 (Table 1), the main lesion was constituted by the presence of areas of sinusoidal dilatation (Figure 1a). These areas were circumscribed and distributed throughout the hepatic lobule, without zonal predominance. These lesions were rare in Patients 3 and 4 and numerous in Patients 1, 2, 5 and 6. In these areas, the sinusoidal lumen was irregularly enlarged and filled with numerous red blood cells. The space of

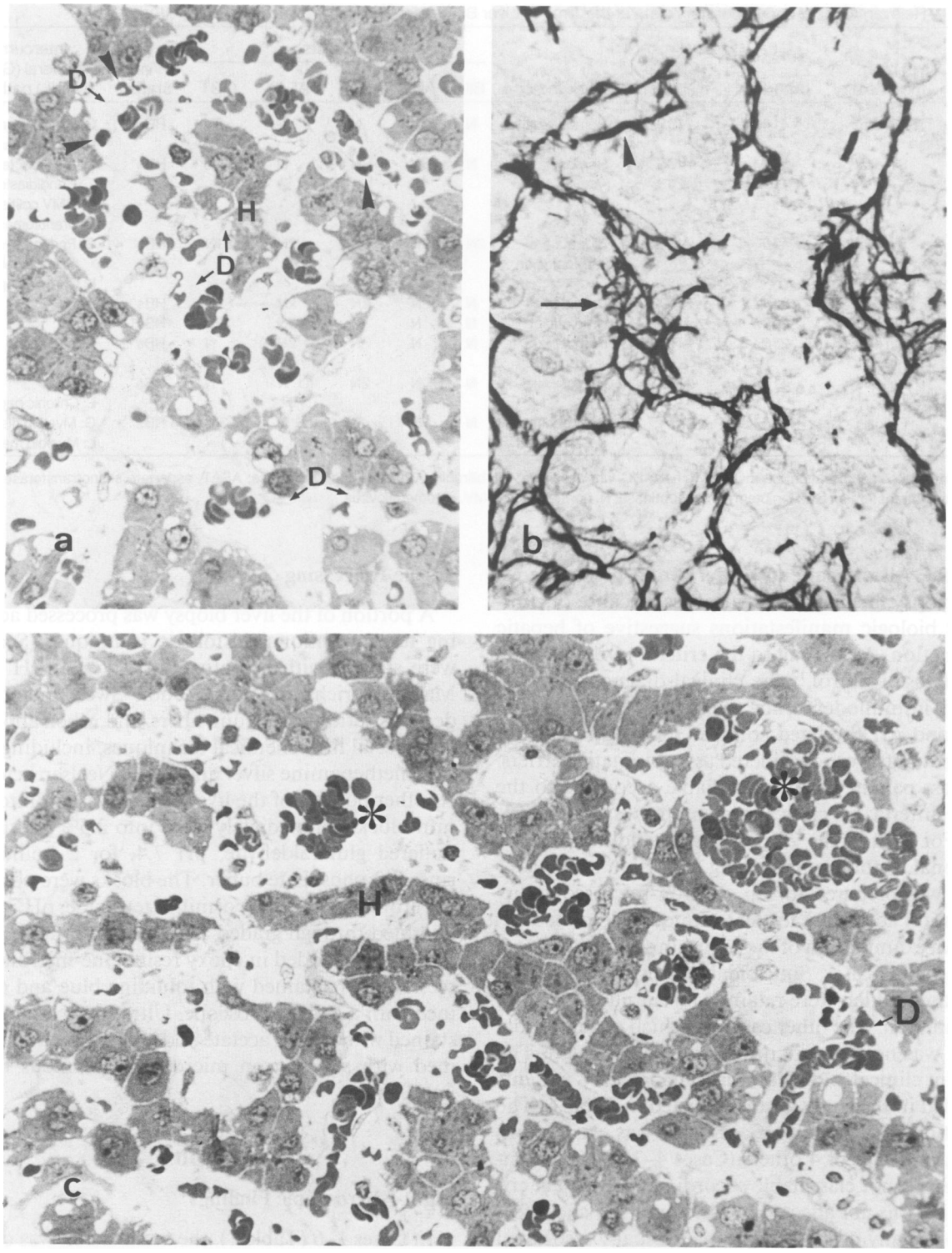


Figure 1—Light-microscopic findings. **a**—Patient 6. In this area of sinusoidal dilatation, the space of Disse (*D*) is enlarged and contains occasional red blood cells (*arrows*). Hepatocytic plates (*H*) are disorganized. (Toluidine blue, semithin section, ×200) **b**—Patient 3. The reticulin framework is disorganized (*arrows*) and sometimes thickened (*arrowheads*) in the areas of sinusoidal dilatation. (Reticulin stain, paraffin section, ×500) **c**—Patient 7. Peliotic cavities (*) filled with red blood cells are observed. When the endothelial lining could be delineated, the space of Disse (*D*) is enlarged and contains numerous red blood cells. The hepatocytic plates (*H*) are compressed and sometimes atrophic. (Toluidine blue, semithin section, ×200)

Disse was moderately enlarged. The reticulin staining demonstrated the presence of moderate amounts of perisinusoidal fibrosis (Figure 1b). Red blood cells were occasionally observed in the perisinusoidal space or between two hepatocytes (Figure 1a). The hepatocytic plates were disorganized.

In Cases 7 and 8 (Table 1), typical peliosis hepatis, characterized by the presence of blood-filled cavities, was observed (Figure 1c). These cavities were randomly distributed throughout the lobule. They were small and occupied only a part of the lobule. The endothelial lining of these cavities was not always visible. When the sinusoidal barrier could be delineated, the space of Disse appeared enlarged and filled with numerous red blood cells (Figure 1c). The hepatocytic plates were disorganized, compressed, and atrophic.

In 5 cases (Patients 1, 2, 3, 7, and 8), the terminal hepatic venules were normal. In 3 cases (Patients 4, 5, and 6), some veins disclosed mild lesions, consisting of the presence of subendothelial red blood cells and of a moderate fibrosis on only a part of the circumference of the vessel wall, without modification of the lumen. Intercurrent histologic findings are tabulated in Table 1.

Electron-Microscopic Findings

The ultrastructural examination confirmed the presence of sinusoidal barrier abnormalities. Features in common to all patients were 1) dilatation of the space of Disse, 2) modifications in the organization of the sinusoidal lining, and 3) morphologic changes in the sinusoidal cells. Varying degrees of dilatation of the space of Disse were observed. In Patients 1–6, limited dilatations were present (Figure 2a). These cavities were often in communication with the sinusoidal lumen through large gaps in endothelial lining (Figure 2b) and in abnormal basement membranes (Figure 2c). Some of them contained erythrocytes or other blood cells (lymphocytes, monocytes, platelets) (Figure 2a). In some instances, a red blood cell was observed inside an endothelial gap, between the sinusoidal lumen and the perisinusoidal space. In Patient 7, a striking and diffuse enlargement of the space of Disse was present (Figure 3). The sinusoidal lumen, often decreased in diameter, was surrounded by a markedly enlarged perisinusoidal space, containing numerous red blood cells. In Patient 8, the space of Disse was usually difficult to delineate because of the disorganization of the endothelial lining (Figure 4). Rare cytoplasmic fragments of endothelial cells were separated by wide gaps, through which red blood cells came in contact with hepatocytes.

Modifications in the structure of the sinusoidal lining were observed not only in areas of peliotic-like changes, but also in areas where no overt dilatation of the sinusoidal lumen was present. Most of the sinusoids were lined by two or more layers (Figure 2a). The outer layer was constituted by endothelial cells surrounded by a basement membrane. This abnormal basement membrane was usually thin and discontinuous (Figure 2c). In many instances, sinusoidal macrophages lined directly a large part of the sinusoidal lumen. The deeper layers constituted a framework in the space of Disse. They could be identified either as cytoplasmic processes of perisinusoidal cells or as elongated expansions of the sinusoidal plasma membrane of hepatocytes. A few cytoplasmic blebs originated from the sinusoidal plasma membrane of hepatocytes. Moderate amounts of collagen fibers were usually present in the space of Disse.

In addition to these peliotic-like changes, various morphologic changes were observed in the different sinusoidal cells. Some endothelial cells showed cytoplasmic swelling and clarification and occasional deposits of lipofuscin granules. In all the patients, endothelial cells also showed the presence of round or elongated cytoplasmic inclusions, containing an electron-dense, sometimes heterogeneous material (Figure 5). Sinusoidal macrophages were always in increased number. They showed an abundant cytoplasm containing numerous lysosomes. Most of them possessed numerous and long cytoplasmic processes which occupied a large part of the sinusoidal lumen (Figure 6). Erythrophagocytosis was frequent (Figure 6). Fat-storing cells were numerous. Most of them were small-sized and contained few lipid droplets, but an abundant rough endoplasmic reticulum.

Hepatocytes were compressed and presented various abnormal shapes. They displayed nonspecific alterations. In the areas of sinusoidal abnormalities, an enlargement of the intercellular space and a moderate dilatation of the bile canaliculi, without modifications of the microvilli or morphologic evidence of cholestasis, were observed. Variable numbers of lipofuscin granules (Figure 3) and giant mitochondria with paracristalline inclusions (Figure 2a) were frequently noted. In Patients 1, 2, and 5, a variable number of lymphocytes was observed in the intercellular space between two hepatocytes. These cells sometimes established close contacts with adjacent hepatocytes, most often through short cytoplasmic expansions or uropods. In Patients 4, 5, and 6, numerous lymphocytes and monocytes were present in the sinusoidal lumen and sometimes in the space of Disse. No contact between leukocytes and sinusoidal cells was observed in any of these patients.

No cellular inclusion suggestive of hepatitis B virus

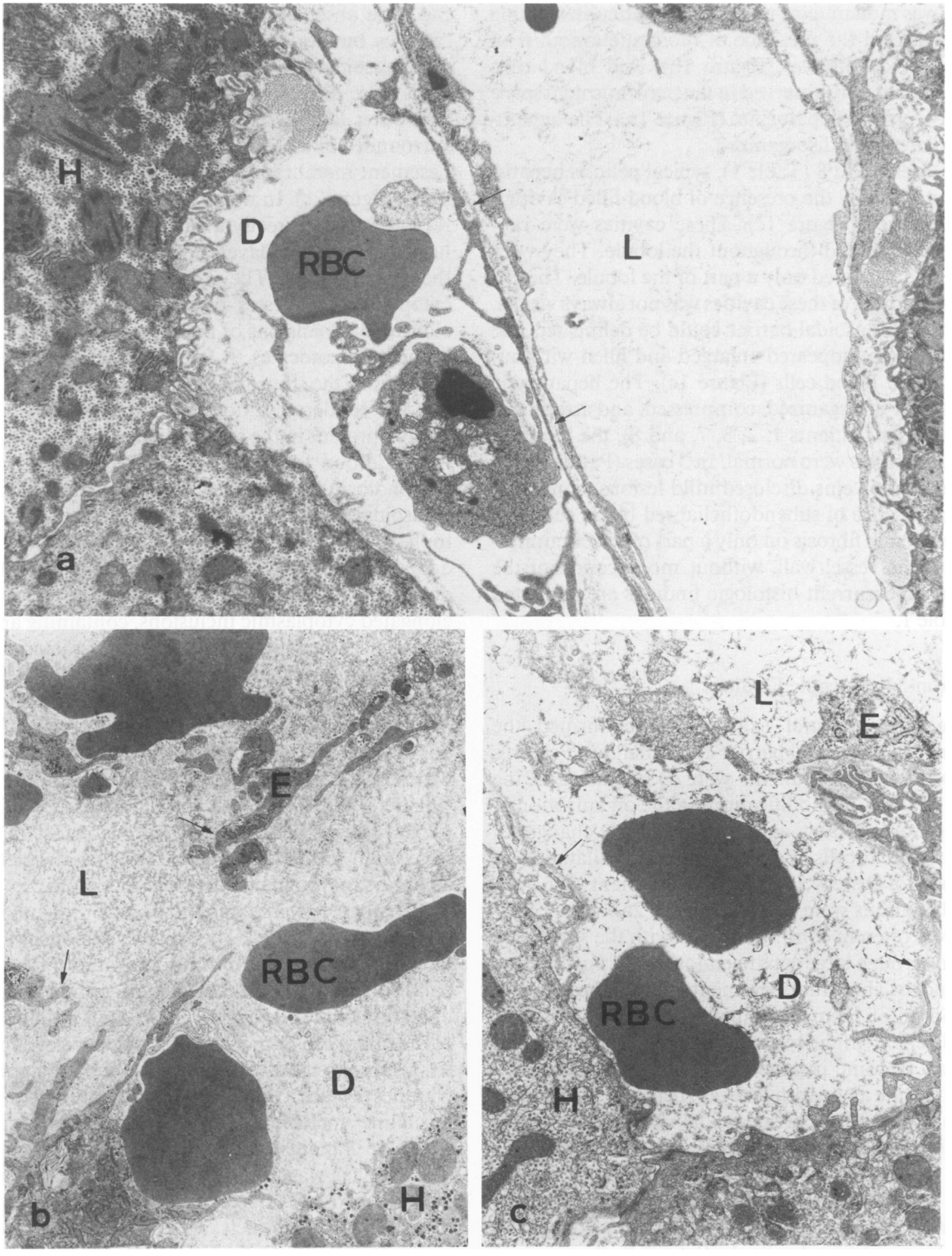
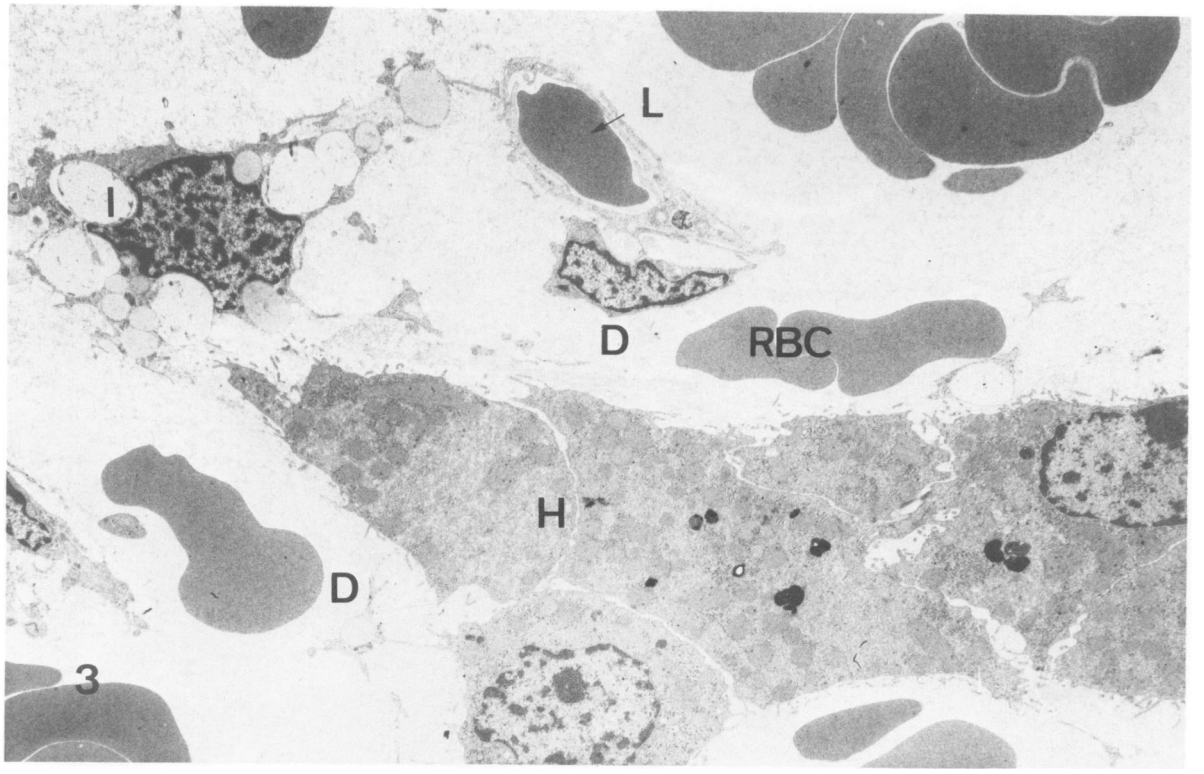


Figure 2—Patient 3. Electron-microscopic findings. **a**—A limited dilatation of the space of Disse (*D*) is figured at low magnification. A red blood cell (*RBC*) is visible inside the space of Disse (*D*). The sinusoidal lining is multilayered and possesses a thin basement membrane (*arrows*). *H*, hepatocytes; *L*, sinusoidal lumen. **b**—In this instance, a large gap (*arrows*) between endothelial cytoplasmic fragments (*E*) results in communication between the space of Disse (*D*) and the sinusoidal lumen (*L*). *H*, hepatocyte. **c**—Red blood cells (*RBC*) come in contact with hepatocytes (*H*) through a discontinuity in an abnormal basement membrane (*arrows*) lining the sinusoidal lumen (*L*). *E*, endothelial cell. (**a**, ×6500; **b**, ×7500; **c**, ×10,000)



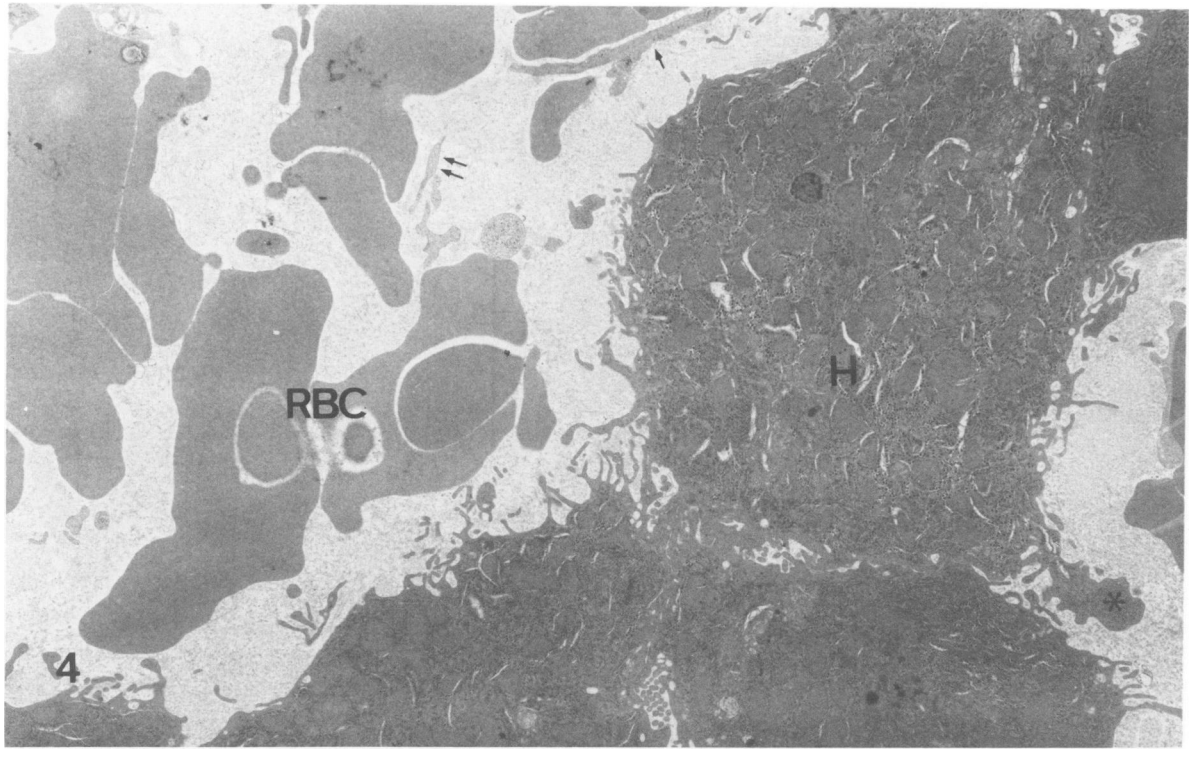
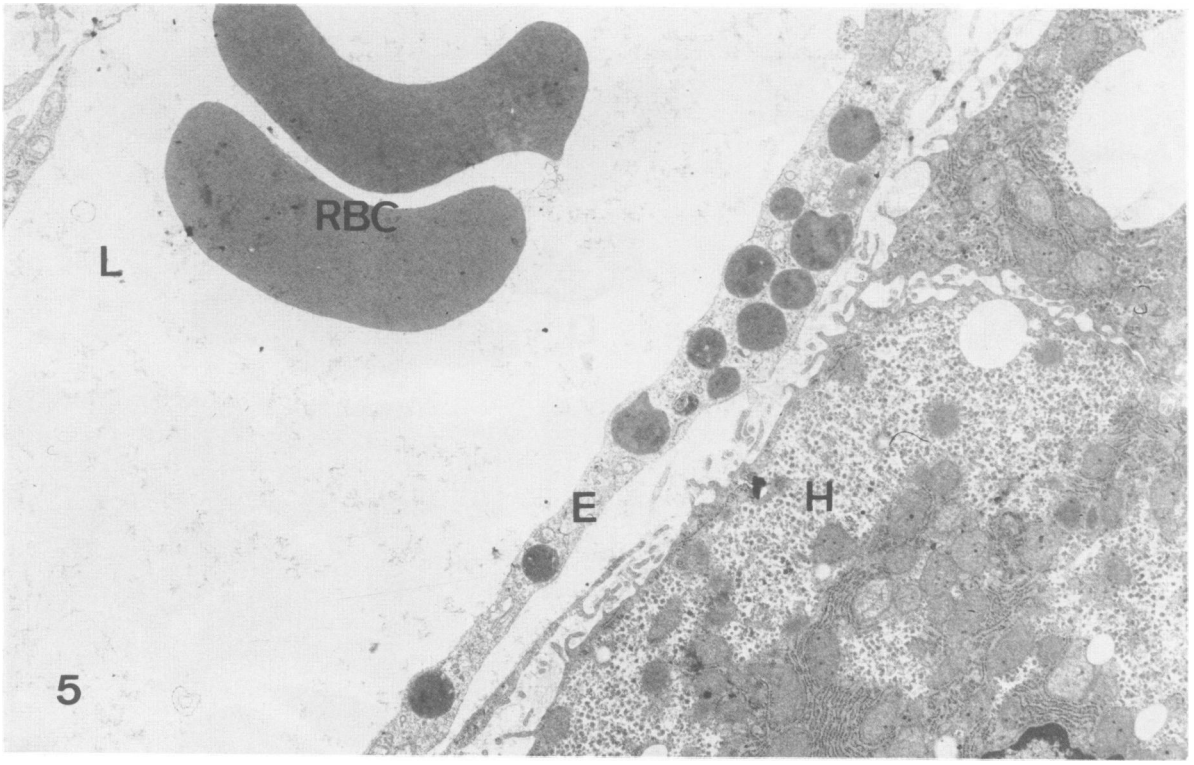


Figure 3—Patient 7. In an area of typical peliosis hepatis, the space of Disse (*D*) is markedly enlarged and contains numerous red blood cells (*RBC*). The sinusoidal lumen (*L*) is decreased in diameter. A fat-storing cell (*I*) is present. The intercellular spaces between the hepatocytes (*H*) are dilated. (×2800) **Figure 4**—Patient 8. In this area of peliosis hepatis, the endothelial lining consists of fragments of endothelial cells (*arrows*) separated by large gaps through which red blood cells (*RBC*) come close to the hepatocytes (*H*). Some blebs (*) originate from the hepatocytic sinusoidal plasma membrane. (×3500)



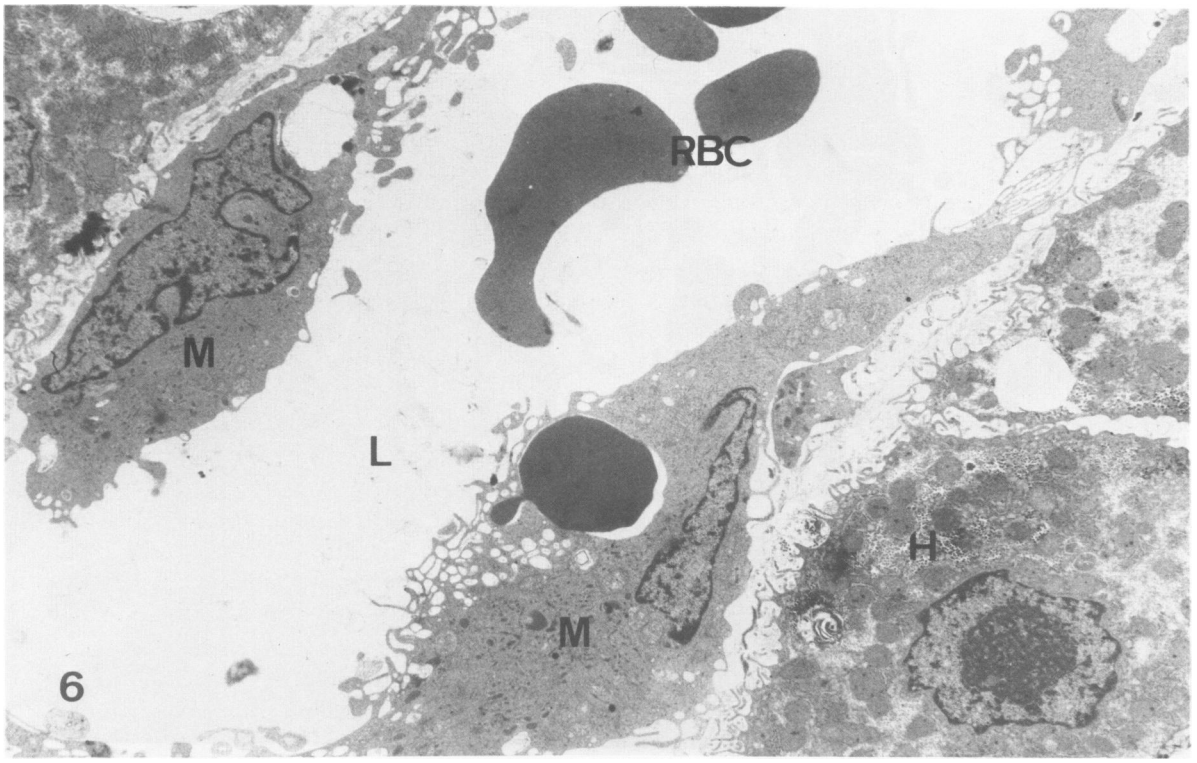


Figure 5—Patient 7. Numerous cytoplasmic inclusions containing an electron-dense material are visible inside an endothelial cell (*E*). *RBC*, red blood cell; *L*, sinusoidal lumen; *H*, hepatocytes. (×12,500) **Figure 6**—Patient 5. Several hyperplastic macrophages (*M*) with numerous pseudopods line a sinusoid. One of them shows evidence of erythrophagocytosis. *RBC*, red blood cells; *L*, sinusoidal lumen; *H*, hepatocytes. (×4500)

infection was identified in any patient. None of the various types of cellular inclusions described during HIV infection, ie, vesicular rosettes, tubuloreticular inclusions, and cylindrical confronting lamellae, was found in this series of patients.

Discussion

The present study is in agreement with two previous reports emphasizing the occurrence of hepatic sinusoidal abnormalities in patients with AIDS. In one of these reports,[8] based on a series of 20 liver biopsies, sinusoidal dilatation was noted in 2 cases and peliosis hepatis in 4. In the other report,[7] based on a series of 36 patients, sinusoidal dilatation was a constant autopsy finding. However, in the other clinicopathologic studies of the liver in HIV infection, the presence of sinusoidal lesions has been noted only incidentally[9,10] or has not been mentioned.[1-6] In the present study group, representative of the various clinical conditions observed in HIV infection, the examination of semithin sections from premortem liver biopsy specimens leads to a diagnosis of sinusoidal lesions, confirmed at the ultrastructural level, in 28% of cases, a relatively high prevalence. Until now, a comparable figure has been reported only in two other groups of patients, patients with aplastic anemia receiving anabolic steroid therapy[15] and recipients of renal transplants.[16]

Certain ultrastructural lesions of the sinusoidal barrier observed in this study closely mimick the changes previously described in peliosis hepatis associated with various conditions: the marked dilatation of the space of Disse, the disruption of the endothelial cell lining, the extravasation of red blood cells, apparently through endothelial gaps, the multilayered cellular lining of the sinusoidal lumen. Such features have been described in tuberculosis, neoplasms, hematologic malignancies, steroid therapy, and organ transplantation,[17,18,19] as well as in peliotic-like changes observed in hypervitaminosis A[20] and in sinusoidal involvement by hairy cell leukemia.[21] However, certain features observed in this series of patients were not previously emphasized. The presence of limited dilatations of the space of Disse communicating with the sinusoidal lumen, a feature not previously described, is particularly noteworthy, because it may be considered as an incipient lesion of the sinusoidal barrier. However, the striking particularity of the sinusoidal abnormalities observed in HIV infection is the presence of numerous and hyperplastic macrophages, often in position of barrier and showing features of active erythrophagocytosis. Our results indicate that this prominent change is not restricted to full-blown AIDS, in which it has been previously reported,[3-6,8] but may also be observed in ARC.

The pathogenesis of peliosis remains a matter of debate. Three hypotheses are currently proposed. First, cystic dilatations of sinusoids may be the result of hepatocellular necrosis and of disruption of the reticulin framework.[23] Second, peliosis hepatis may be the consequence of a congestion of sinusoids secondary to a blockade of liver blood outflow.[16] Last, peliosis hepatis may be the result of a direct lesion of the sinusoidal barrier.[19] The morphologic and experimental data favoring the last hypothesis have been already extensively discussed.[19] The present observations further reinforce this concept. No major changes of the hepatocytes or of the centrilobular veins were observed. The ultrastructural observations suggest that the spectrum of sinusoidal lesions observed in this series of patients corresponds to varying degrees of the same basic process involving a direct injury of the endothelial lining. As previously stated,[19] the disorganization of endothelial lining is usually not accompanied by significant degenerative changes in endothelial cells. The dense cytoplasmic inclusions frequently noted in this study appear specific neither of HIV infection nor of peliotic-like changes. The same features have been previously described in various conditions, including acute hepatitis,[23] chronic active hepatitis of unspecified origin,[24] and cholestasis,[25] and in endothelial cells maintained in primary cultures.[26]

Chronic wasting diseases, merely chronic infections and advanced neoplasms, and adverse effects of various drugs and toxins are the most frequent causes of liver sinusoidal lesions, including sinusoidal dilatation and peliosis hepatis.[14,18,19,22] Four of our patients presented an intercurrent pathology which is a potential cause of sinusoidal abnormalities: cachexia, granulomatous hepatitis,[27] or a myelopoliferative disorder.[28] However, the remaining 4 patients presented none of the many etiologic factors known to be associated with the occurrence of liver sinusoidal barrier lesions. In particular, they received none of the drugs incriminated in the pathogenesis of these lesions.[14] Therefore, while a previously unreported adverse drug effect cannot be definitely excluded, our observations raise the possibility that a relation may exist between HIV and hepatic sinusoidal lesions.

This hypothesis is further strengthened by the fact that, to our knowledge, sinusoidal lesions have not been previously described in infections caused by human hepatotropic viruses. In particular, sinusoidal dilatation and peliosis hepatis have not been reported in the various types of viral hepatitis for which HIV-seropositive patients are also at risk: hepatitis B,[16] hepatitis non-A, non-B,[29] and hepatitis delta.[30] An associ-

ation between a viral infection and the occurrence of sinusoidal lesions is known only in the rat. In this species, experimental induction of peliosis hepatis by the 9-H leukemia virus has been reported.[31]

Several mechanisms may explain how HIV infection may lead to a hepatic sinusoidal injury. A direct cytopathic effect of HIV on endothelial cells may be hypothesized, because liver endothelial cells are known to be sensitive to viral infections.[32] However, that endothelial cells are actually infected by HIV remains to be demonstrated. An indirect cytopathic effect mediated by inflammatory and/or immune cells may be also speculated. Potentially toxic soluble factors are known to be released by activated sinusoidal macrophages[33] and by cytotoxic T lymphocytes. Morphologic support for these hypotheses is brought by the presence of hyperplastic sinusoidal macrophages in HIV-infected patients and by the demonstration of a sinusoidal infiltration by $CD8^+$ lymphocytes, at least in some cases of AIDS.[5] A speculative hypothesis may be raised. In HIV infection, the liver sinusoidal abnormalities may be the consequence of an abnormal immunologic response, related to the inappropriate secretion of immunoregulatory factors acting on vascular endothelium. This hypothesis has been postulated to explain the high prevalence of Kaposi's sarcoma, a tumor of probable vascular endothelial origin,[34] in transplant recipients[35] and in AIDS.[36]

In conclusion, HIV infection is associated with a significant incidence of hepatic sinusoidal abnormalities, including peliosis hepatis, sinusoidal dilatation, and perisinusoidal fibrosis. The ultrastructural lesions of the sinusoidal barrier observed in this condition are reminiscent of the changes induced by other etiologic factors. The sinusoidal lesions were observed in the various clinical conditions associated with HIV infection. The association is unlikely to be fortuitous. An injury of the endothelial cells directly or indirectly related to the presence of HIV may be implicated in the pathogenesis of these lesions, either as a main factor or as an additional factor associated with intercurrent causes.

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