The pathology of human Lassa fever

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Pathological findings have been described in only a small number of cases of Lassa fever since the virus was first isolated in 1969. Morphologically, eosinophilic necrosis of hepatocytes was the most frequent finding and focal necroses, often extensive, were present in most cases. These findings are similar to the lesions previously described in Argentinian and Bolivian haemorrhagic fever. Focal interstitial pneumonitis, focal tubular necrosis in the kidney, lymphocytic infiltration of the splenic veins, and partial replacement of the splenic follicles by amorphous eosinophilic material have been described, but the significance of these findings is unclear. More detailed and sophisticated investigations are required in the future if pathogenetic mechanisms are to be unravelled.

INTRODUCTION

In the 6 years since the initial description of Lassa fever, outbreaks have been documented in several West African countries, and the theoretical hazard of importation into other continents has been realized. Information about the pathology and pathogenesis of the disease remains fragmentary, however. Descriptions have been given of post-mortem examinations, including gross and microscopic pathology, performed on 2 cases from the initial outbreak in Jos, Nigeria (1), 2 cases from the 1970 outbreak in Jos (2), and 3 cases from the 1972 epidemic in Liberia (3). The description of the Liberian cases was limited to the hepatic pathology. Ultrastructural findings in a case from the 1972 Sierra Leone epidemic were also limited to the liver (4).

Despite the paucity of autopsied cases, the existing reports do represent a well documented sample. Lassa virus was isolated from the Sierra Leone case and in all 4 of the Nigerian autopsies. Of the 4 cases considered by Sarrat et al. (3), one was confirmed as Lassa fever by isolation of the virus and 2 were presumed to be Lassa fever, on the basis of clinical, epidemiological, and pathological findings. A fourth case from the outbreak was excluded by the authors, because the autopsy showed pathological evidence of malaria. The potential contribution of coincident disease to the pathological lesions must be faced constantly, even in virologically documented cases of Lassa fever.

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We have reviewed the published cases and obtained some of the microscopic material through the courtesy of Drs Edington and Robin. In addition, Dr Jacinto Gochoco, Jr, of York Hospital, York, Pennsylvania, has made available to us material from a case of laboratory-associated infection. The pathological findings on this last case have not been reported previously; Lassa virus was isolated from blood antemortem.

GROSS PATHOLOGICAL FINDINGS

As in many other viral diseases, the gross pathology in Lassa fever is unimpressive compared to the dramatic clinical course and mortality rate. Constant but nonspecific findings include congestion of the viscera, oedema of the soft tissue, and petechiae, especially in the gastrointestinal tract. Pleural effusions have been present in most cases, and ascites has been noted clinically. Luminal blood in the small intestine was described in one case; massive bleeding sufficient to produce clinical shock does not appear to have been present. The kidneys of two cases were described as swollen or haemorrhagic and nodular, but microscopic evidence of tubular necrosis has been minimal.

Neuropathological findings are available only on the case from York, Pennsylvania. The brain was normal in weight. The meningeal blood vessels were congested. Oedema of the true and false vocal cords was also noted; the terminal events in this case began with acute respiratory distress and probable laryngospasm, for which a tracheotomy was performed.

MICROSCOPIC PATHOLOGY

Complete microscopic descriptions are available for 4 of the autopsies; the hepatic pathology has been studied in an additional 4 cases.

Heart. Congestion and slight interstitial oedema were present and in one instance slight nonspecific epicardial infiltrates were noted. No microscopic evidence of myocarditis has been described.

Lungs. Congestion and oedema without significant haemorrhage were present. Edington (2) described interstitial pneumonitis with mononuclear cells and megakaryocytes in 2 cases. In the York case there was focal interstitial accumulation of mononuclear cells; many of these were in capillaries, however, and a classical interstitial pneumonia was not present.

Kidneys. Occasional focal tubular and glomerular necroses were described by Edington et al. (2) in one case. Three cases showed congestion, autolysis, and occasional hyaline or pigment casts. Typical ischaemic nephrosis has not been described.

Spleen. Congestion and atrophy of the white pulp have been noted. Deposition of amorphous eosinophilic material in the white pulp was present in several cases. In the York case, this material replaced cells at the periphery of the follicles, occasionally circumferentially (Fig. 1). Infiltration of the intima of splenic veins by lymphoid cells has been noted in most cases.

Lymph nodes. Few comments have been recorded on lymph node histology. In one of the original cases, follicles were depleted and histiocytes with phagocytosed nuclear debris were present. The lymph nodes in the York case were enlarged and cellular, but no germinal centres were seen. Occasional erythrophagocytosis was observed. The histopathological findings were neither distinctive nor specific.

Gastrointestinal tract. The findings, which are nonspecific, include petechiae and chronic inflammation, especially in the mucosa.

Brain. Information is available only on the York autopsy. No evidence of haemorrhage, meningitis, or encephalitis was seen.

Miscellaneous. No significant pathological findings have been described in other organs. Small lymphocytic accumulations were present in the adrenals of the York case; necrosis was not present. Neither vasculitis nor fibrin thrombi in small blood vessels have been observed in any organ.

Liver. Data on the liver are more complete than on any other organ, and the hepatic pathology has been most distinctive. Even with the small number of cases at hand, there is evidence of a spectrum of severity in the hepatitis produced by Lassa virus. Some of the livers have shown slight to moderate fatty metamorphosis; fatty change has not been a constant finding and it may be entirely unrelated to Lassa infection. Similarly, a mononuclear portal infiltrate is so frequently present at autopsy that the significance of this finding is difficult to evaluate.

From a histological standpoint the liver is the main target organ in human Lassa infection. Every case autopsied so far has contained eosinophilic or shrinkage necrosis of individual hepatocytes, and larger foci of hepatocellular destruction have been observed frequently. Single liver cells in an otherwise intact cord undergo eosinophilic change, similar to that classically described in yellow fever. The cytoplasm becomes focally condensed, producing an eosinophilic cytoplasmic inclusion. Other cells show homogeneous eosinophilic cytoplasmic staining, with pyknosis or disappearance of the nucleus (Fig. 2). Fragments of such cells appear free in the sinusoids or phagocytosed in Kupffer cells. These Councilman-like bodies contain prominent vacuoles.

The frequency of focal hepatic necrosis has also been emphasized in the previously published reports. Small foci of necrosis are scattered through the lobules without zonal distribution. Usually, but not invariably, they are associated with eosinophilic necrosis in the surrounding hepatocytes (Fig. 3). Some necrotic areas are marked only by haemorrhage and cell loss. With one exception, the cases that have been confirmed virologically have exhibited coalescence of necrotic foci, which bridge portal and central areas of the lobule. In the least severely involved livers, occasional portal and central zones are connected by cell necrosis. Where the damage is more extensive, multiple portal-to-portal and portal-to-central necrotic " bridges " are present and large portions of individual lobules may be destroyed (Fig. 4). Even in these areas, however, the reticulin framework of the liver remains intact. Collapse of the supporting stroma is not present (Fig. 5). The amount of inflammation is small and is not related to the extent of hepatocellular damage. Polymorphonuclear leukocytes and mononuclear cells are scattered through the sinusoids. The latter are difficult to distinguish from hyperplastic Kupffer cells, which are also prominent.

One documented exception to the pattern of

Fig. 1. Circumferential deposition of amorphous eosinophilic material in the white pulp of the spleen. This material did not stain with amyloid stains. H & E.

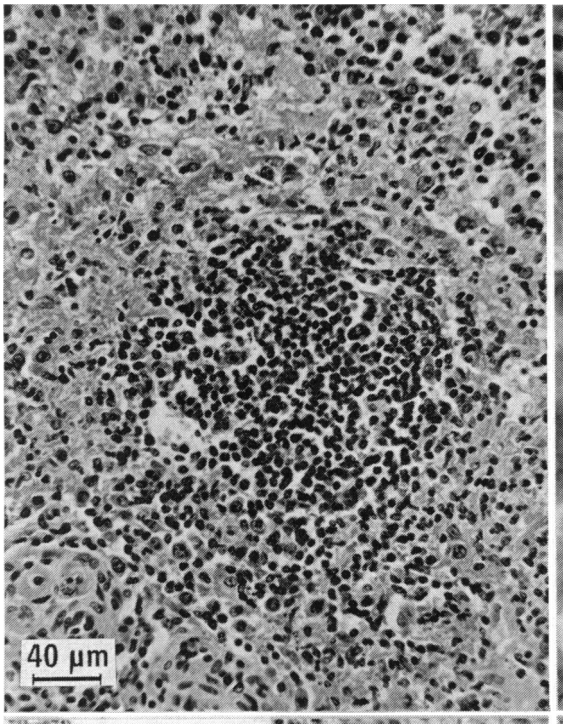
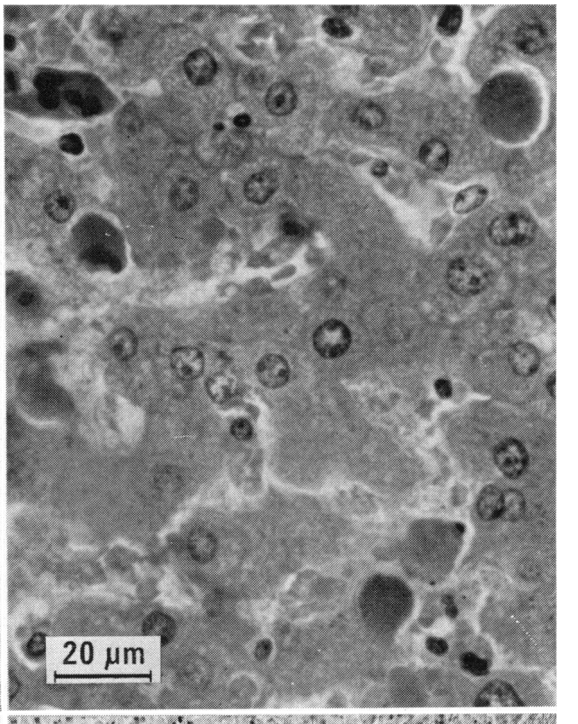


Fig. 2. Councilman-like bodies in Lassa fever. Rounded, dense, eosinophilic cells are located in the hepatic cords and sinusoids. Focal eosinophilic change in the cytoplasm of hepatocytes is also present. H & E.



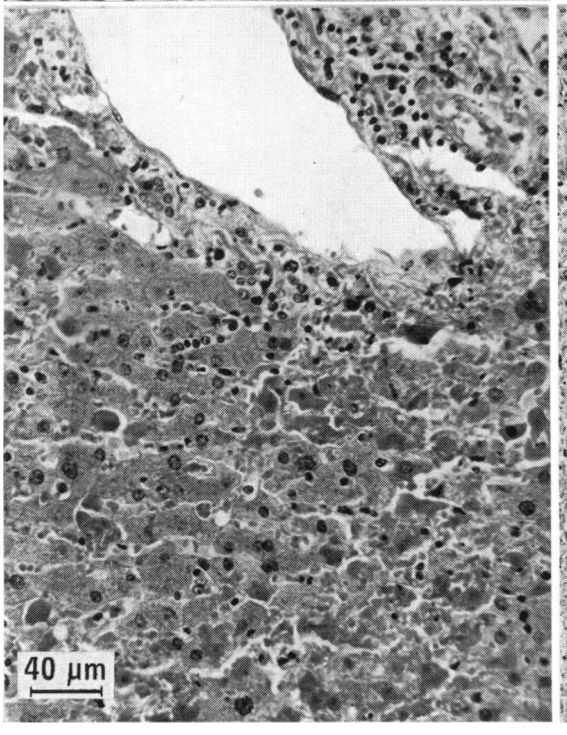


Fig. 3. Focal hepatic necrosis associated with eosinophilia of the surrounding hepatocytes and Councilman-like bodies. There is no zonal distribution to the necrosis. H & E.

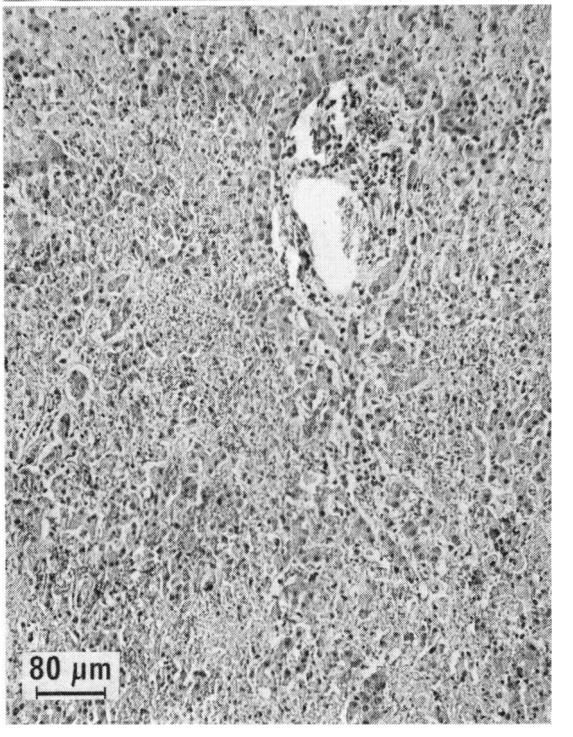
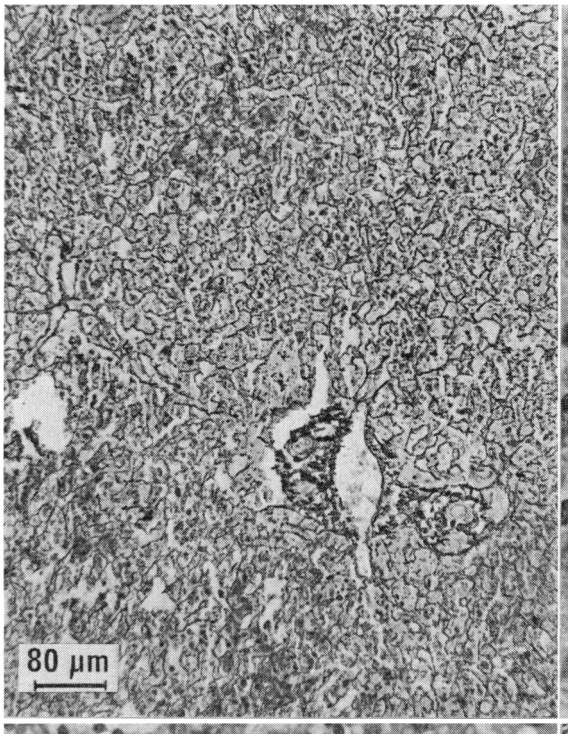
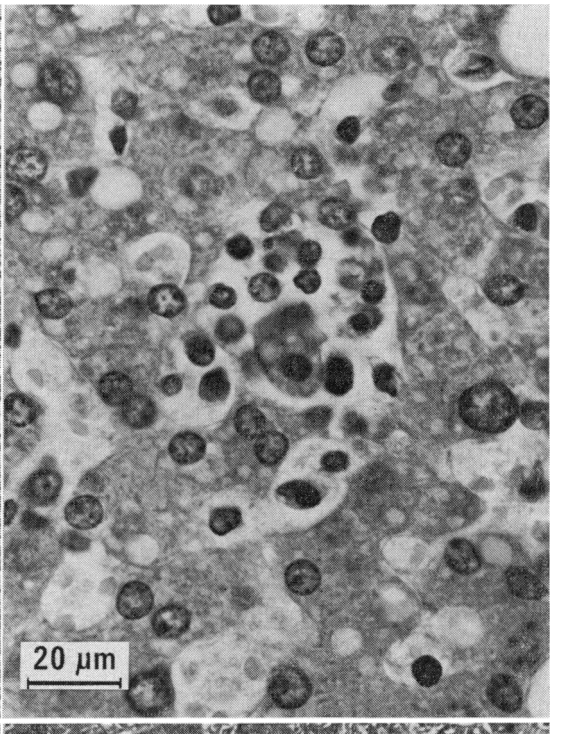


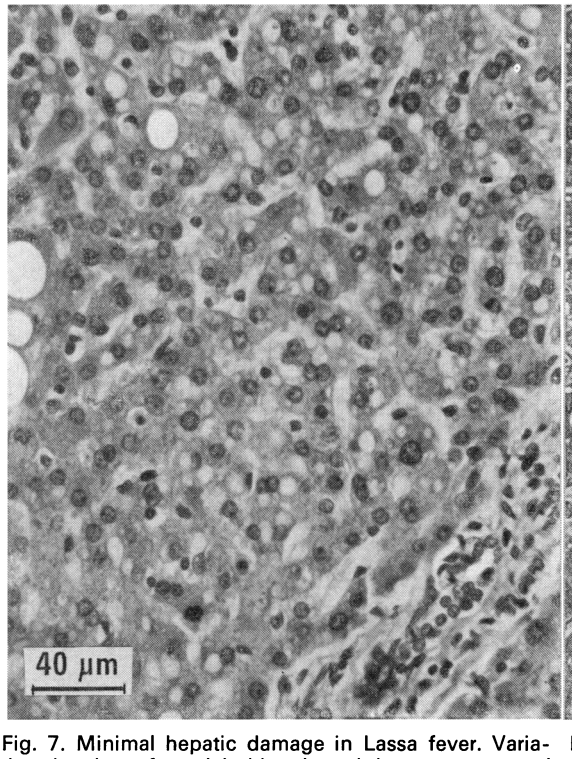
Fig. 4. Coalescence of hepatic necrosis to involve most of the lobule. Surviving hepatocytes showed eosinophilic change, but Councilman-like bodies are not evident. H & E.

Fig. 5. Intact reticulin framework of the liver in an area of extensive necrosis. Same field as Fig. 4 in an adjacent section. Wilder's reticulin stain.

Fig. 6. Single vacuolated hepatocyte undergoing acidophilic necrosis. Mononuclear sinusoidal infiltrate is concentrated around this cell. H & E.







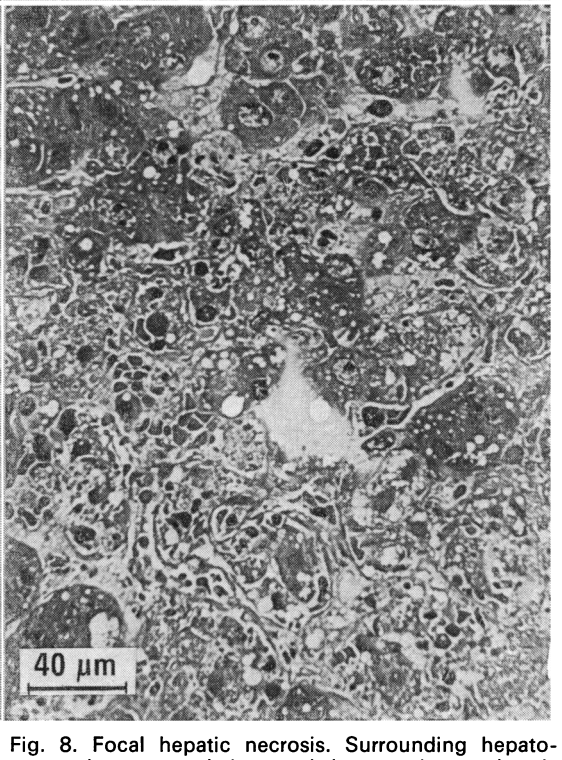
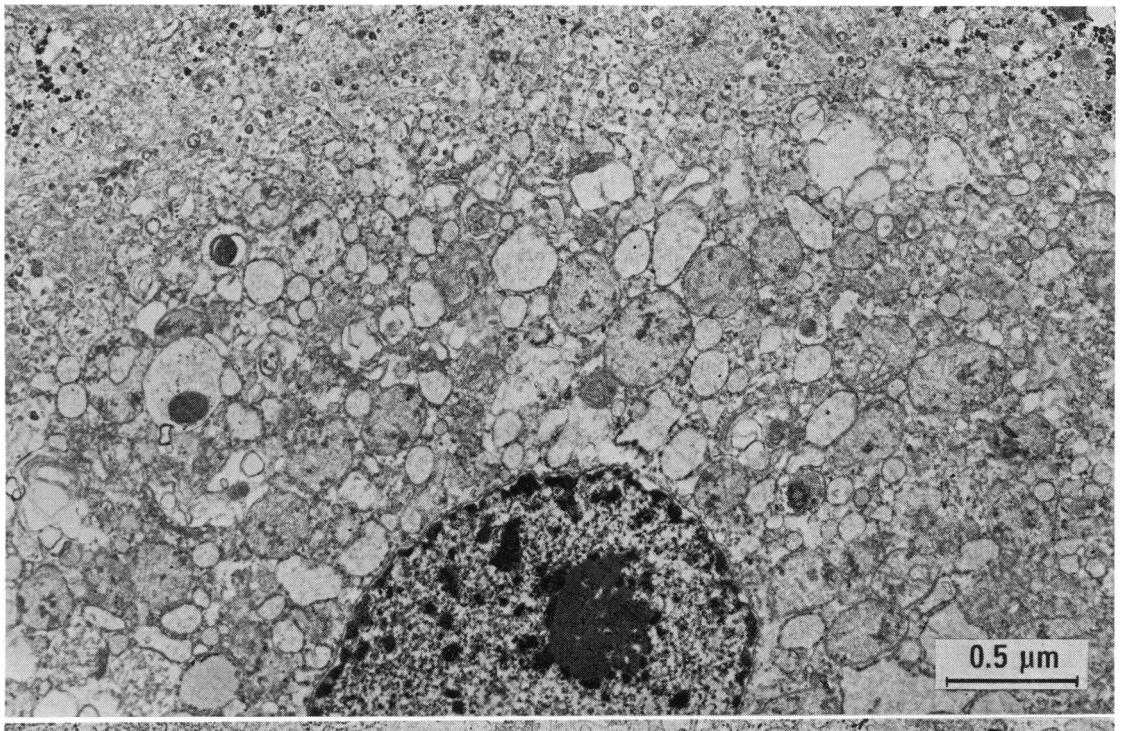


Fig. 7. Minimal hepatic damage in Lassa fever. Variation in size of nuclei, binucleated hepatocytes, and mitotic figures are present. H & E.

Fig. 8. Focal hepatic necrosis. Surrounding hepatocytes show vacuolation and increased cytoplasmic density. They do not represent classical Councilman-like bodies, but do resemble the eosinophilic cells seen in paraffin sections. Toluidine blue.

Fig. 9. Degenerating hepatocyte with dilated rough endoplasmic reticulum and flocculent densities within mitochondria. Numerous Lassa virions are present along the cell membrane. Lead citrate-uranyl acetate.



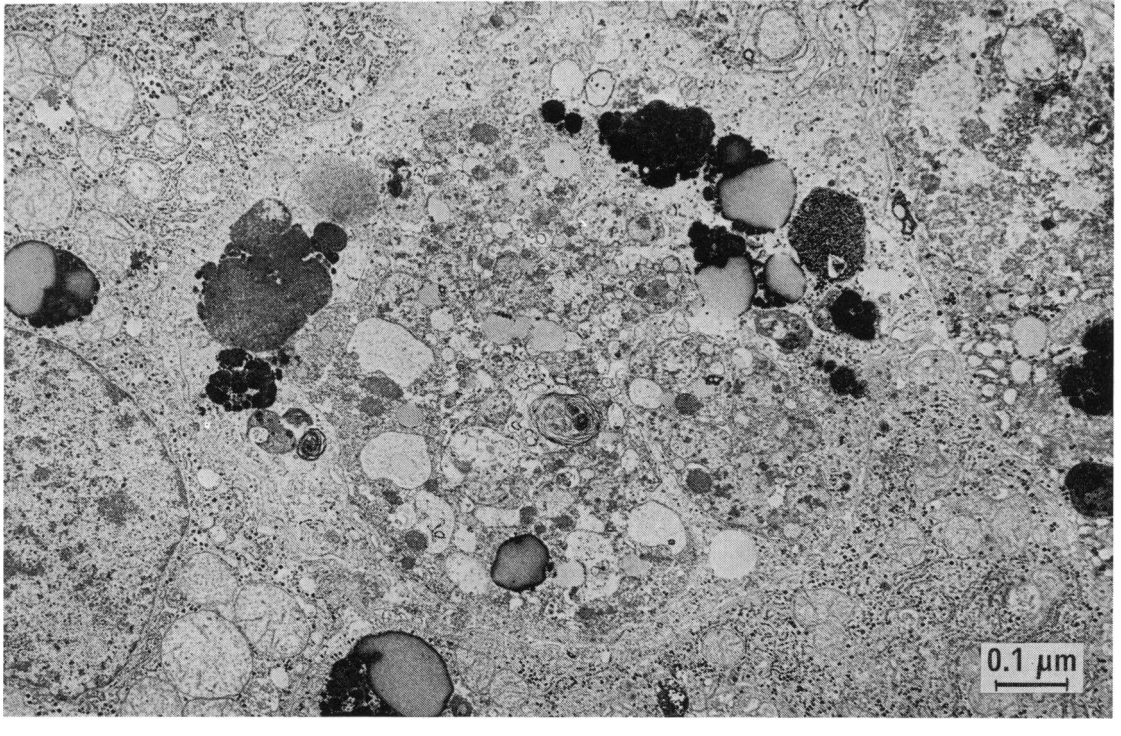


Fig. 10. Rounded portion of an hepatocyte showing cytoplasmic degeneration. This cell probably represents one of the Councilman-like bodies observed in paraffin sections. Lead citrate-uranyl acetate.

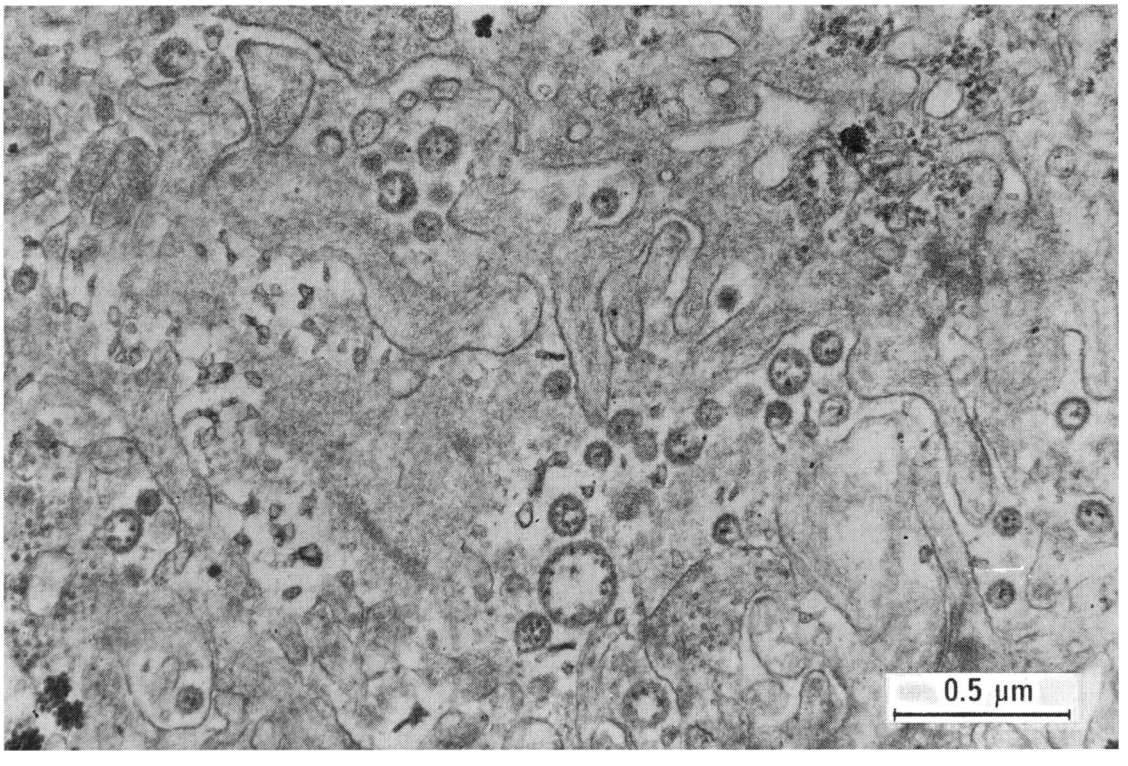


Fig. 11. Numerous typical Lassa virions are present in the extracellular space between the microvilli of an hepatocyte. Lead citrate-uranyl acetate.

necrosis is represented by the York autopsy. In this case, rare acidophilic change was observed, involving single, scattered hepatocytes. Clear vacuoles, consistent with the presence of lipid, were present in these cells also. A moderate mononuclear infiltrate was present throughout the sinusoids; in one focus, the infiltrate was accentuated around an eosinophilic hepatocyte (Fig. 6). Multicellular foci of necrosis were not observed. In contrast to the other cases, binucleated liver cells and numerous mitotic figures were observed (Fig. 7). These findings suggest hepatic injury and attempts at regeneration.

A case of intermediate severity is included in those reported by Sarrat et al. (3). The liver showed extensive acidophilic change without concentration into necrotic foci. Again there was no zonal localization. Although the case was not confirmed virologically, it occurred as part of a documented Lassa fever epidemic and histologically it falls into the middle of a spectrum of damage observed in proved cases.

Ultrastructural studies of Lassa fever have been hampered by lack of facilities for electron microscopy in the epidemic areas and inadequate fixation when attempts have been made to evaluate the specimens in reference laboratories (2). An excellently preserved liver biopsy was obtained from one patient in the Sierra Leone epidemic (4). Thick sections for light microscopy revealed foci of necrosis, similar to those previously described, except that classical Councilman bodies were rarely observed (Fig. 8).

Damaged cells were vacuolated and cell boundaries were often blurred. Portions of a few dense cells, having the appearance of Councilman bodies, were present in Kupffer cells. The majority of affected hepatocytes, however, showed some increased density, but did not demonstrate the remarkable condensation of classical acidophilic necrosis. These findings were confirmed ultrastructurally. Dilatation of the endoplasmic reticulum and accumulation of flocculent electron-dense material in swollen mitochondria were the most common findings (Fig. 9). Areas of focal cytoplasmic degeneration were frequently found. Rounded cells or portions of cells, showing the increased electron density associated with focal cellular degeneration, were also observed (Fig. 10), but the classical cytoplasmic condensation of acidophilic necrosis was observed only in a few phagocytosed cell fragments. As had been observed with the light microscope, undamaged hepatocytes were often adjacent to severely damaged cells.

The most instructive finding in the ultrastructural study was the demonstration of large numbers of typical arenavirus particles. Although Lassa virus had been isolated antemortem, the demonstration of virions in relation to the pathological lesion confirmed the specificity of the lesions that had been observed in the light microscope. Virions were always found in association with hepatocytes rather than with Kupffer cells (Fig. 11). Interestingly, they were more frequent in areas where cell damage was less severe. Because Lassa virus matures by budding from cell membranes, intact host cells are required for production of viral particles. No ribosomal aggregates, suggestive of arenavirus inclusions, were seen.

DISCUSSION

In a systemic viral infection, such as Lassa fever, classical histopathology often contributes to the initial understanding of the disease, but definition of pathogenetic mechanisms requires the addition of complementary techniques. Although the number of cases for consideration is small, they fortunately represent a select and well documented group. The uniformity of the findings reinforces the impression that we are dealing with a minimum of background noise from coincident diseases. A review of the currently available pathological data demonstrates a major site of tissue damage in the liver and outlines several other areas that deserve further study.

The similarities between the pathology of Lassa fever and that of Bolivian and Argentinian haemorrhagic fever (BHF and AHF) have been noted by other authors. The pathogenesis of these infections in man is not known, but research in each may be applicable to the others. Comparison of the reported pathology in the South American haemorrhagic fevers with the data on Lassa fever and with the information that Walker et al. (5) have obtained in subhuman primates infected with Lassa virus provides interesting parallels (Table 1). Child et al. (6) described the autopsies of 8 patients with BHF. The livers of all 8 cases showed Kupffer cell hyperplasia with erythrophagocytosis and acidophilic necrosis of hepatocytes. In addition, two cases showed foci of necrosis, similar to the hepatic necrosis observed in the Lassa cases. Similarly, the description of AHF by Elsner et al. (7) includes Kupffer cell hyperplasia, acidophilic Councilman-like bodies, and, in 5 out of 12 cases, the presence of focal, non-zonal necrosis.

The liver is undoubtedly a major target organ for Lassa virus and the pattern of hepatic necrosis

Table 1. Histopathologic findings in human arenavirus infections

Organ	Lesion	No. of times lesions observed/No. of cases examined		
		Lassa fever	Bolivian haemorrhagic fever (6)	Argentine haemorrhagic fever (7)
Heart	Myocarditis	0/4	not described	4/12
Lung	Interstitial pneumonitis or hyaline membrane formation	2/4	6/6	4/12
Kidney	Tubular necrosis	1/4	2/8	6/12
Spleen	Deposition of eosinophilic material in white pulp	3/4	0/8	0/12
Brain	Lymphocytic infiltrate or microglial proliferation	0/1	6/6	5/12
Liver	Eosinophilic necrosis of hepatocytes	8/8	7/7	7/12
	Multicellular foci of hepatic necrosis	6/8	2/7	5/12

produced appears to be characteristic of human arenavirus infections. Nevertheless, other infections and toxins may produce a similar type of hepatic necrosis; the differential diagnosis has been discussed by Sarrat et al. (3), and an excellent set of slides demonstrating the histopathological differentiation from yellow fever is available from the Armed Forces Institute of Pathology, Washington, D.C. (set No. L-15274). The non-zonal distribution of the necrosis differentiates Lassa virus hepatitis from the classical yellow fever lesion. We do wonder, however, as Porterfield (8) did, whether cases of Lassa fever occurring before the characterization of the virus may have been mistaken for yellow fever. The vacuolar character of the acidophilic necrosis mimics that of yellow fever and the lobular distribution may be difficult to evaluate when necrosis is extensive. Although acidophilic bodies have been demonstrated in viral hepatitis, the most frequent form of hepatocellular damage is " ballooning " degeneration, which is not seen in Lassa virus hepatitis. The integrity of the hepatic reticulin framework is another potentially important difference in the hepatic damage seen in viral hepatitis and Lassa virus hepatitis. " Bridging " eosinophilic necrosis was seen in the more severely damaged livers of Lassa fever patients. This pattern of hepatic necrosis in viral hepatitis has been reported by Boyer & Klatskin (9) to correlate with poor prognosis and the development of chronic liver disease. In viral hepatitis, this " bridging " necrosis is associated with collapse of the reticulin framework of the liver, but in Lassa fever, as in yellow fever, the reticulin remains intact even in severely damaged lobules. One would predict that the subsequent development of cirrhosis in Lassa fever would be rare, as it is in yellow fever.

Other clinical differential diagnoses, such as malaria and typhoid fever, are not a major problem in the pathological diagnosis. However, an additional differential problem in African patients has been introduced by a recent case of haemorrhagic fever with hepatic necrosis caused by Marburg virus. The extensive eosinophilic necrosis of hepatocytes and non-zonal distribution of the lesions suggested a diagnosis of Lassa fever before the isolation of the virus established the diagnosis.

In several of the autopsied cases of Lassa fever, hepatic necrosis has been sufficiently extensive to suggest hepatic failure as a major contributor to the fatal outcome. In the available cases, however, there is no correlation of the extent or severity of hepatic damage with the duration of disease. Extensive necrosis is not related either to overwhelming, rapidly fatal infection or to prolonged infection, in which more extensive tissue damage might be seen histologically. This lack of correlation is emphasized by the virtual absence of necrosis in the York autopsy and in the squirrel monkeys experimentally infected with Lassa virus.

The nature of the acidophilic necrosis found in Lassa fever requires further investigation. The ultrastructure of acidophilic necrosis has been described

in experimental yellow fever (10), in viral hepatitis (11), and in formalin-fixed tissue from a case of BHF (12). In the single ultrastructural investigation of Lassa fever reported (4), classic acidophilic necrosis was rare and sampling problems were considered a possible explanation. Examination of the haematoxylin-eosin-stained sections from other cases suggests that the material examined ultrastructurally was, in fact, typical and that the majority of dense hepatocytes seen in Lassa fever are caused by extensive cytoplasmic degeneration and accumulation of electron-dense material in cell organelles. Combination of histochemical studies on formalin-fixed tissue with ultrastructural examination of glutaraldehyde-fixed tissue may resolve this question in future cases.

Except for the liver pathology, the accumulated pathological data provide little help in constructing a pathogenetic scheme. From clinical and epidemiological data, the most likely portals of entry appear to be cuts or abrasions of the skin or the upper respiratory tract. Viral multiplication in the oropharyngeal lymphoid tissue or regional nodes probably occurs before the documented viraemia. Pharyngitis, which is so prominent clinically, has not been studied pathologically and routine autopsy material would be unlikely to contribute significant information. Focal interstitial pneumonitis, which has been observed in a few cases of Lassa fever and more frequently in AHF and BHF, could result from direct respiratory infection or from viraemia. The pneumonitis does not appear to be clinically significant, but more data are needed.

After viraemia is established, multiple organs are probably involved, but there is little evidence of morphological damage. Because of the frequency of myocarditis in AHF and the severe inflammation found in the myocardium of one of the monkeys infected with Lassa virus (5), clinical and pathological signs of myocarditis should be sought in the future. Tubular necrosis in the kidney is difficult to evaluate because of the concurrent hepatic necrosis and shock; the possibility of primary or secondary renal involvement requires more attention, however. In particular, more neuropathological data are needed. Information is available on only one brain, and no inflammation was seen. The presence of neurological symptons and the documentation of cerebral inflammation in AHF, BHF, and experimental Lassa fever emphasize the necessity for further examination of the central nervous system. We should be mindful that the prototype virus of the group, lymphocytic choriomeningitis (LCM) virus, may produce inflammatory lesions of the brain in man, and that the second documented death from LCM occurred in a patient who had acquired the infection while assisting at the autopsy of the first (13). Many of the neurological symptoms described could be metabolic in origin, and morphological studies have an important contribution to make in this area.

Attention has been focused on the vascular system and on coagulation mechanisms in a number of haemorrhagic fevers. Fibrin thrombi, which are the morphological correlate of intravascular coagulation, have not yet been found. Their absence does not, however, exclude the presence of a consumption coagulopathy. The demonstration of segmental vasculitis, resembling polyarteritis nodosa, in the squirrel monkeys provides a clue that should be considered in future autopsy studies. Vasculitis has not yet been observed in Lassa fever, but segmental vascular lesions are often difficult to demonstrate.

Finally, immunological participation in the pathogenesis of Lassa fever must be considered. The lymph nodes demonstrate reactive changes, but no specific lesions. In the spleen, partial replacement of the white pulp by eosinophilic material has been a frequently observed lesion in human Lassa fever. A similar lesion has been documented in experimental Lassa fever (5) and in experimental BHF (14). Although cellular necrosis is not seen, the material presumably replaces lymphocytes. The relationship of this finding and of the absence of germinal centres to the delayed humoral antibody response is intriguing. The status of cellular immunity is unknown, but the periarteriolar areas in the spleen and the paracortical regions of the lymph nodes are intact. Subintimal infiltration of splenic veins by lymphocytes is probably a nonspecific result of the lymphoid hyperplasia. Such infiltration is prominent in leukaemia and has been noted in healthy people (15). It was also observed in the recent South African case of Marburg disease.

In the final analysis, cell damage may be mediated by immune mechanisms or by direct viral cytopathology. Experimental infections with various arenaviruses have provided dramatic evidence of immunopathological tissue damage. Because cell membranes are altered during the maturation of Lassa virus, the infected cells could present a target for sensitized lymphocytes. The possibility that in man necrosis is a direct effect of viral infection cannot be dismissed, however. In the liver, for instance, extensive hepatocellular damage and numerous virions are present

with minimal inflammatory response. Of the autopsy cases studied thus far, the most impressive hepatic inflammatory response was seen in the York case, in which evidence of cell damage was minimal.

For the future, a " modern " autopsy with the addition of adequate electron microscopy, organ-specific viral titration, studies of cell-mediated immunity to Lassa virus antigen, and immunofluorescence would have tremendous potential for elucidating the complexities of pathogenetic mechanisms. Major problems will have to be solved; resources at the site of epidemics will have to be coordinated with distant reference facilities. In particular, the hazard of cryostat sectioning must be circumvented.

RÉSUMÉ

PATHOLOGIE DE LA FIÈVRE DE LASSA CHEZ L'HOMME

Le virus de la fièvre de Lassa a été isolé et caractérisé pour la première fois en 1969. Pendant les six années qui ont suivi, les études pathologiques sur ce virus ont été peu nombreuses. Des rapports complets d'autopsie (non compris le cerveau) n'ont été établis que dans quatre cas et la pathologie du foie n'a été étudiée que dans quatre autres cas. Les cas signalés ainsi qu'un cas d'infection contractée en laboratoire ont fait l'objet de comptes rendus dans les revues spécialisées.

La pathologie macroscopique de la fièvre de Lassa n'a rien de très frappant, rien de spécifique. On a signalé des œdèmes, de la congestion, des hémorragies pétéchiales et des épanchements sérieux. L'étude microscopique par contre révèle que le foie est l'organe le plus fortement atteint. On a constaté dans tous les cas une nécrose acidophile et, dans beaucoup de cas, une nécrose focale, souvent très étendue. Dans une étude de l'ultrastructure, on a trouvé des virions de la fièvre de Lassa associés à des hépatocytes endommagés, d'où l'on peut semble-t-il conclure que l'accroissement de la densité cellulaire observée dans des coupes en paraffine est dû pour une grande partie à une dégénérescence cytoplasmique focale et à l'accumulation de matière dense dans les organites cellulaires. Dans les autres organes, on a notamment constaté des dépôts de matière éosinophile amorphe dans la pulpe blanche de la rate, une infiltration lymphocytaire des veines spléniques, une pneumonie interstitielle focale (2 cas sur 4) et une nécrose tubulaire focale (1 cas sur 4).

Si l'on compare la fièvre de Lassa avec d'autres fièvres hémorragiques à arénavirus, on constate que la nécrose hépatique est un trait caractéristique mais non le seul. Il conviendrait à l'avenir d'étudier les lésions du myocarde et du cerveau; au niveau de ces deux organes, on a trouvé des lésions pathologiques dans la fièvre hémorragique d'Argentine et la fièvre de Lassa expérimentale, mais on n'a pas constaté d'anomalies — ou du moins on ne les a pas étudiées — dans la fièvre de Lassa chez l'homme.

L'atteinte hépatique peut hâter l'issue fatale dans certains cas, mais ne saurait être seule mise en cause. Des études cliniques, immunopathologiques et ultrastructurelles seraient nécessaires pour élucider la pathogenèse de la fièvre de Lassa, et notamment le rôle éventuel des lésions tissulaires d'origine immunologique.

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DISCUSSION

HOTCHIN: There seems to be a general tendency to regard LCM and perhaps other arenaviral diseases as being mediated by cellular immunity. I have seen two patients treated with LCM virus for terminal cancer, both of them anergic individuals. They developed progressively higher viraemia, were unable to mount an antibody response, and both died. The pathological findings were reminiscent of those you have just described, including pneumonitis. Moreover, acute LCM infection of mice produces both hepatitis and ascitic fluid. If you take the ascitic fluid and inject it into normal mice, it kills them in about 30 seconds. Preliminary information suggests that there is a substance like bradykinin in this fluid. The possibility exists that there are toxic or pharmacological mediators that play a role in these diseases.

WINN: I agree with your comment about cellular immunity. We simply do not have the data to determine the cause of cell damage. The possibility of direct viral damage cannot be eliminated. The parallels between Lassa fever and the few fatal cases of LCM disease are interesting, but we have no information to offer on possible chemical mediators.

COLES: [a] I am a little puzzled by your statement that the liver is the major target organ in Lassa fever, since I cannot recall a single patient seen in Sierra Leone who has been jaundiced.

WINN: Your comment reinforces our belief that more neuropathological data are badly needed. Many of the clinical symptoms might be metabolic in origin and future autopsy studies will help to determine if there is meningitis. The liver is the main target organ from the histopathological standpoint. There may well be other organs that are severely damaged functionally but show minimal histological changes.

RUSSELL: The findings of peritoneal and pleural effusions in Lassa fever, with an apparent increase in vascular permeability in the absence of histopathological changes in the vessels, appear to be similar to those in dengue haemorrhagic fever. In this disease the increased vascular permeability is due to activation of the complement system with resultant production of C3a and C5a anaphylotoxins, which cause histamine release. An early clue to this mechanism was the observation that mast cells appeared degranulated in autopsy and biopsy specimens. Have mast cells been carefully examined in autopsy material from Lassa fever and do they appear degranulated? There are also similarities in liver pathology. Patchy paracentral hepatic necrosis is seen in dengue haemorrhagic fever. The two diseases might be difficult to differentiate in the absence of virological studies.

WINN: To my knowledge mast cells have not been looked at specifically and most of our material has been selected by haematoxylin-eosin stained sections. There are a few paraffin blocks available and we shall look at the mast cells in those tissues. The pathological findings in Lassa fever are quite similar to those described in the group B arbovirus haemorrhagic fevers, including dengue and Kyasanur Forest disease. I have little experience with those diseases, but it is my impression that the hepatic necrosis is much less extensive than that seen in Lassa fever.

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