Susceptibility and Resistance of Inbred Strains of Syrian Golden Hamsters (Mesocricetus auratus) to Wasting Disease Caused by Lymphocytic Choriomeningitis Virus: Pathogenesis of Lethal and Non-lethal Infections

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SUMMARY

In different strains of inbred Syrian golden hamsters (Mesocricetus auratus), the lymphocytic choriomeningitis virus (LCMV) strains WE and Armstrong (ARM) produced systemic infection with infective virus and viral antigens detected predominantly in reticuloendothelial organs. Host and virus strain-dependent fatal wasting disease also occurred. After infection with WE, all MHA and PD4 hamsters died of a progressive wasting disease and infectivity persisted in organs at relatively high titres. LSH and CB strain hamsters resisted lethal disease and totally eliminated infection. LVG and LHC strain hamsters were intermediate in susceptibility to WE; some died of wasting and had persistently infected organs, while others cleared infection and survived. ARM was avirulent causing an inapparent infection in all hamsters. LCMV antibody responses were temporally comparable for all hamsters with either lethal or non-lethal infection. Histologically, lymphoid hyperplasia and low-grade systemic perivascular mononuclear leukocyte infiltration were found in all LCMV-infected hamsters. However, non-necrotic segmental ileal changes, which included vascular congestion, minimal haemorrhage and crypt epithelial growth extension into the intestinal wall, were found in susceptible hamsters when infected with the lethal WE strain.

INTRODUCTION

Lymphocytic choriomeningitis virus (LCMV) infections of Syrian golden hamsters (Mesocricetus auratus) have been long recognized (Smadel & Wall, 1942), and a concern in the epidemiology of human LCMV outbreaks (Ackermann, 1973; Skinner & Knight, 1979). Although hamster LCMV infections were largely regarded as inapparent, benign and immunizing (Smadel & Wall, 1942; Volkert & Hannover Larsen, 1965; Parker et al., 1976), episodes of lethal and non-lethal illness in LCMV-inoculated hamsters have been mentioned in these reports and in other studies (Rhodes & Chapman, 1950; Förster & WachENDORFER, 1973; Thacker et al., 1982). As there has been little research using hamsters as model hosts for LCMV pathogenesis and immunity studies, hamster illness and fatalities by LCMV have been ignored and many parameters of the host–virus interaction in hamster LCMV infections have not been examined.

The development of appropriate rodent host models for the study of human arenavirus haemorrhagic fevers has been a continuing programme in our laboratory (Peters et al., 1987). In this regard, we have examined host–virus relationships that might be involved in LCMV-induced disease in hamsters. Using inbred strains of Syrian golden hamsters, models of fatal disease and of inapparent non-lethal infection caused by LCMV were established (Genovesi &
Peters, 1987a, b). Mortality and illness for hamsters were shown to be host and virus strain-dependent. Inbred MHA and PD4 hamsters were all susceptible to LCMV strain WE infection with symptoms of severe wasting, dehydration and diarrhoea followed by death. Inbred LSH and CB hamsters resisted death and disease caused by WE. LHC and LVG hamsters were intermediate in susceptibility to WE, and showed a range of signs from severe lethal wasting to minimal non-lethal illness or no overt disease. The Armstrong (ARM) strain of LCMV, in contrast to WE, was avirulent for all hamsters. Because of the uniform strain-dependent mortality responses of hamsters to LCMV, this host–virus system should be suitable for further experimental pathogenesis and immunity studies. We continued our investigation to include a temporal study of lethal and non-lethal LCMV infections in inbred hamsters inoculated with either the virulent WE strain or the avirulent ARM strain. LCMV infection patterns, organ involvement, host LCMV antibody responses and histological changes were described.

**METHODS**

**LCMV stocks.** LCMV strains WE (Rivers & Scott, 1936) and ARM (Armstrong & Lillie, 1934) were obtained from Dr W. E. Kirk (Department of Microbiology, Medical Center, West Virginia University, Morgantown, W.Va., U.S.A.). Both strains were plaque-purified and propagated in BHK-21 cells, and stocks were stored at −70 °C (Genovesi & Peters, 1987a, b).

**Plaque assay for infective LCMV.** For prepared virus, and blood and organ homogenates of LCMV-inoculated animals. LCMV infectivity was measured in p.f.u. in a Vero cell monolayer–agarose overlay system (Jahrling & Eddy, 1980; Genovesi & Peters, 1987a,b). Infective LCMV titres are expressed as mean log10 p.f.u. ± S.E.M. per g or per ml of sample groups. Due to assay limitations, blood samples that were regarded as negative for infective LCMV were recorded with titres of 0-7 log10 p.f.u./ml. Organ homogenates that were regarded as negative for infectivity were recorded with titres of 1.7 log10 p.f.u./g.

**Animals and preparation of tissue samples for virological, serological and histological evaluation.** Female *M. auratus* of the inbred strains CB/SsLak, LHC/Lak, LSH/SsLak, MHA/SsLak, PD4/Lak and random colony-bred Lak : LVG(SYR) were reared under barrier conditions at the Lakeview Hamster Colony (Newfield, N.J., U.S.A.), and purchased at 8 to 10 weeks of age from Charles River Breeding Laboratories (Wilmington, Mass., U.S.A.). The strains were called CB, LHC, LSH, MHA, PD4 and LVG respectively. All animals were housed in P-3 laboratory containment facilities in air-filtered cages and fed and watered freely. Sentinel uninoculated guinea-pigs and hamsters, maintained in the same facility in separate cages to LCMV-inoculated animals, did not develop LCMV infection or serum LCMV antibody during the course of these studies. Before use all animals were kept isolated for 2 weeks, and then tested and found to be seronegative for LCMV.

At 10 to 12 weeks of age hamsters were inoculated intraperitoneally (i.p.) with 3.3 log10 p.f.u. of either WE or ARM in 0.2 ml and then routinely monitored for body weight, signs of illness, and mortality. Where indicated, inoculated and uninoculated age-matched hamsters were serially bled or sacrificed for their organs. Blood samples were drawn from the retro-orbital sinus of CO2 gas-anaesthetized animals into heparinized tubes and stored at −70 °C until used for infective LCMV assay. Sera for LCMV antibody assay were drawn from clotted blood and stored at −20 °C.

For infective LCMV assay, organs of sacrificed animals were weighed, homogenized, clarified and stored at −70 °C. Bone marrow specimens, obtained from each individual animal by pooling pulp excised from hind leg femoral and tibial bones, were also weighed, homogenized and stored at −70 °C.

For preparation of standard histological sections and staining with haematoxylin and eosin (H&E), organ samples from LCMV-inoculated and age-matched uninoculated hamsters were fixed in 10% neutral buffered formalin.

Tissues were examined for LCMV antigens by direct immunofluorescence (Jahrling & Eddy, 1980). Organs, frozen in a polyethylene glycol compound at −70 °C, were cut using a cryostat into tissue sections and acetone-fixed onto glass slides. The fixed tissue samples were then directly stained with fluorescein isothiocyanate (FITC)-conjugated LCMV immunoglobulins that had been raised in guinea-pigs. All slides were viewed for LCMV immunofluorescence under a microscope with an ultraviolet light-source.

**LCMV antibody assays.** Sera were heated at 56 °C for 30 min and tested for LCMV antibody by an indirect immunofluorescent antibody test (IFAT) and in an in vitro assay for neutralizing antibody, using a constant-serum varied-virus format (Jahrling & Eddy, 1980; Peters et al., 1987). Details of both procedures were previously reported (Genovesi & Peters, 1987a, b). The endpoint serum IFAT titre was the final serum dilution that gave positive binding to slide-fixed LCMV-infected cells in an immunofluorescence reaction with an FITC conjugate of goat IgG anti-hamster gamma-globulin. The serum IFAT titre is expressed as the mean reciprocal log10 dilution ± 1 S.E.M. for sample groups. Serum samples that were negative for antibody by this procedure were reported (Genovesi & Peters, 1987). The endpoint serum IFAT titre was the final serum dilution that gave positive binding to slide-fixed LCMV-infected cells in an immunofluorescence reaction with an FITC conjugate of goat IgG anti-hamster gamma-globulin. The serum IFAT titre is expressed as the mean reciprocal log10 dilution ± 1 S.E.M. for sample groups. Serum samples that were negative for antibody by this procedure were...
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recorded with IFAT titres of 0-7 (-log10). LCMV-neutralizing antibody was determined as the logarithmic reduction in the plaque titre of a standard LCMV stock, caused by a fixed concentration of a test hamster serum and guinea-pig complement. LCMV antibody titre is expressed as a mean log10 neutralization index (LNI) ± 1 S.E.M. for experimental animal groups. Serum samples that were negative for LCMV antibody were recorded with LNI titres of 0-7.

RESULTS AND DISCUSSION

Disease, infection and humoral immunity in LCMV-inoculated hamsters

Body weight changes, viraemia and LCMV antibody responses of WE-inoculated animals are depicted in Fig. 1 for lethal disease-susceptible inbred MHA hamsters, in Fig. 2 for lethal disease-resistant inbred LSH hamsters, and in Fig. 3 for LVG hamsters of intermediate susceptibility to lethal LCMV disease. Changes in these parameters, following inoculation of the inbred hamsters with ARM, are summarized in Table 1.

A resolving and immunizing acute systemic viral infection with an early host antibody response was generally observed in all hamsters inoculated with either WE (Fig. 1 to 4) or ARM (Table 1). By 3 days post-inoculation (p.i.) with WE (Fig. 1 to 3) a comparable viraemia of 4-0 to 4-5 log10 p.f.u./ml was detected in all hamster strains. By 7 days p.i. viraemia in WE-infected susceptible MHA hamsters was increased and remained elevated 14 days p.i. at a titre of about 6-0 log10 p.f.u./ml (Fig. 1). At peak viraemia (7 to 14 days p.i.), the major clinical manifestations of WE-induced wasting disease, which included progressive weight loss, lethargy, dehydration and some diarrhoea, had begun and continued to the death of all inoculated animals (7 to 30 days p.i.). In lethally infected MHA hamsters, serum IFAT antibody was detected by 7 days p.i. with titres of 1-9 (-log10), and IFAT titres continued to rise thereafter. By 21 to 28 days p.i., all moribund MHA hamsters had serum neutralizing antibodies to LCMV with LNI titres of about 1-2. From 14 to 28 days p.i., when antibody titres were increasing, viraemia significantly declined, but was never totally eliminated.

Inbred LSH (Fig. 2) and CB (not shown) hamsters were fully resistant to wasting disease and death by WE infection. Following WE inoculation, there was no decrease in body weight. From 3 to 7 days p.i., viraemia did not significantly increase (Fig. 2), as compared to the viraemias of the lethally infected MHA hamsters (Fig. 1). After 7 days p.i. viraemia declined and was no longer detected by 21 to 28 days p.i. The antibody response (IFAT and LNI) of the resistant LSH hamsters, during acute WE infection (3 to 28 days p.i.), was quite similar in magnitude and kinetics (Fig. 2) to that of the lethally infected MHA hamsters (Fig. 1). After the end of viraemia (28 days p.i.) in the non-lethally infected LSH hamster, serum IFAT and LNI antibodies had further increased to respective titres of >3-5 (-log10) and 3-0 (Fig. 2) and remained elevated for up to 60 days p.i. These animals were not viraemic (data not shown).

Disease and mortality responses of WE-infected LVG (Fig. 3) and LHC (not shown) hamsters were heterogeneous. Over 60% of WE-infected LVG hamsters died of severe wasting illness with progressive weight loss between 7 and 30 days p.i. Remaining LVG hamsters survived acute infection with minimal or no signs of disease, as reflected in the average body weight gain by 28 days p.i. Although by 7 days p.i. the mean viraemia titre for the LVG hamsters was 5-3 log10 p.f.u./ml, infective blood titres ranged from 4-0 to 6-5 log10 p.f.u./ml (Fig. 3). These titres overlapped the viraemia ranges of the susceptible MHA hamsters, 5-5 to 7-0 log10 p.f.u./ml (Fig. 1), and of the disease-resistant LSH hamsters, 3-5 to 5-0 log10 p.f.u./ml (Fig. 2). As shown for MHA hamsters, the onset of lethal disease was evident from 7 to 14 days p.i. in the infected cohort of LVG hamsters with the higher viraemia ranges. In the lethally infected LVG hamsters, viraemia persisted from 7 to 28 days p.i. at titres higher than those of the hamsters with non-lethal WE infection. LCMV antibody (IFAT and LNI) response in LVG hamsters with WE infection (Fig. 3) was comparable to the other hamster strains (Fig. 1, 2). Also, along with the increased serum antibody titres after 7 days p.i., viraemia decreased and was not detected in the surviving cohort of LVG hamsters by 35 days p.i. (Fig. 3).

Following ARM inoculation all hamsters, regardless of strain did not exhibit illness and gained weight (Table 1). These hamsters also produced serum IFAT and LNI antibodies that increased in time with titres nearly identical to those of WE-infected hamsters. Although acute
Fig. 1. Course of LCMV infection in inbred adult female MHA hamsters susceptible to lethal disease. Hamsters, inoculated i.p. with $3.3 \log_{10}$ p.f.u. of WE, were monitored for body weight (g ± S.E.M.). Blood samples were tested for virus (○) and serum was tested for LCMV antibody by IFAT (▲) and LNI (■). Thirty-eight animals were tested 0 and 3 days p.i. and 31, 21, 12 and five animals were tested at 7, 14, 21 and 28 days p.i., respectively.

Fig. 2. Course of LCMV strain WE infection in inbred adult female LSH hamsters resistant to lethal disease. For details see Fig. 1 legend. Forty-two animals were tested 0 and 3 days p.i. and 36, 30, 24, 18, 12 and eight animals were tested at 7, 14, 21, 28, 35 and 42 days p.i., respectively.

Fig. 3. Course of LCMV infection in adult female LVG hamsters of intermediate susceptibility to lethal disease caused by WE. For details see Fig. 1 legend. Sixty-seven animals were tested 0 and 3 days p.i. and 58, 46, 24, 11 and eight animals were tested at 7, 14, 21, 28 and 35 days p.i., respectively.
viraemia was detected in all ARM-inoculated hamsters (Table 1), infective virus was rapidly eliminated between 14 and 21 days p.i. (data not shown) and was always temporally lower than those of hamsters with either lethal or non-lethal WE infection.

Lethal and non-lethal LCMV infections in different strains of hamster were further studied to determine systemic involvement. Organ samples were homogenized and assayed for infectivity (Fig. 4), and tissue sections were processed for LCMV antigen detection by direct immunofluorescent staining. Reticuloendothelial organs, in particular the bone marrow, appeared to be early primary viral replication sites in all WE-infected hamsters (Fig. 4). Initial bone marrow infectivity titres (3 to 7 days p.i.) directly paralleled the respective clinical response of the three groups of hamster strains. From 3 to 7 days p.i., peak infectivity titres in the bone marrow of the susceptible MHA hamster strain were significantly higher than those of the disease-resistant LSH hamsters or the partially susceptible LVG hamsters (Fig. 4). Although after this time, bone marrow infectivity of all hamster strains declined, those of the lethally infected MHA hamsters persisted at relatively elevated titres. By 21 to 35 days p.i., respectively, bone marrow infectivity could no longer be detected in any surviving LSH or LVG hamster.

As for other organs of the WE-infected hamsters, spleen, brain, liver, lung, kidney, urinary bladder (Fig. 4), adrenal glands and uterus (data not shown) appeared to be sites of early blood-borne dissemination of virus and secondary virus replication. Infectivity titres in these organs were more elevated and persistent in the susceptible MHA hamsters than in the resistant LSH hamsters. In the latter group of animals, infectivity was not detected after 21 days p.i. For LVG hamsters (Fig. 4), infectivity in these organs was comparable in duration and relative content to that of the MHA hamsters during acute WE infection (3 to 28 days p.i.). By 28 to 35 days p.i. virus was no longer detected in LVG survivors.

Infective LCMV was also recovered from the thymus, salivary glands, heart, trachea and oesophagus of all hamsters. However, these organs did not appear to be major virus replication sites as infectivity was nearly equal to the blood titre of the respective hamster strain (not shown).

During peak WE viraemia (7 days p.i.), infective LCMV in the small intestines (Fig. 4), stomach, caecum, large intestines and pancreas (not shown) did not reach the titres in the other organs of MHA and LSH hamsters. (LVG hamsters were not tested for virus in these organs.) In these organs of the susceptible MHA hamsters, infective LCMV was detected at about 3·0 to 4·0 \log_{10} \text{p.f.u./g} from 7 to 21 days p.i. Infectivity fell by 28 days p.i. to 2·0 to 2·5 \log_{10} \text{p.f.u./g}. In disease-resistant LSH hamsters infectivity was barely detected.
Fig. 4. Infective virus content of organs during WE infection of female adult hamsters of different strains: LSH (▲), highly resistant to WE; LVG (●), intermediate in susceptibility to WE; MHA (■), highly susceptible to WE. On the days following i.p. inoculation with 3.3 log₁₀ p.f.u. of WE, hamsters were sacrificed and organs sampled for infectivity as follows: (a) blood, (b) bone marrow, (c) spleen, (d) brain, (e) liver, (f) lung, (g) kidney, (h) urinary bladder, (i) small intestine. Data at all time points are based on groups of six to eight animals.

The systemic distribution of infective WE, as noted for the inbred hamsters (Fig. 4), and as described in prior reports of hamster LCMV infections (Smadel & Wall, 1942; Rhodes & Chapman, 1950; Parker et al., 1976; Skinner & Knight, 1979; Thacker et al., 1982), might suggest that the virus is pantropic. In our study LCMV antigens were found by direct immunofluorescence in most organs examined from hamsters with acute WE infection. Intense focal staining was present in tissue sections from the liver (Fig. 5), spleen, uterus, brain, kidneys, lungs and adrenal glands (not shown). Relatively less intense immunofluorescent staining was noted in the thymus, salivary glands and the heart. (The organs of the alimentary canal and the pancreas were not prepared for immunofluorescence examination.) In general, the ease of viral antigen demonstration by immunofluorescence tended to correlate with infectivity titres. As infectivity diminished, LCMV antigen detectability declined. LCMV antigens could not be found in organs from any surviving hamster. LCMV antigen distribution in the organs of ARM-infected hamsters was the same as for the WE-infected hamsters, except that fewer antigen-positive foci were visualized.

The overall tissue distribution of LCMV antigens was not qualitatively different among the hamster strains. LCMV has a wide host range in cell culture, infecting a variety of mammalian cells such as fibroblasts, neural, lymphoid and macrophage cells without cytocidal effect, but has a marked predilection to replicate in cells of the lympho-reticuloendothelial system in vivo (Wilsnack & Rowe, 1964; Mims & Subrahmanyan, 1966; Lehmann-Grube et al., 1975;
Fig. 5. LCMV-specific immunofluorescent staining of liver from a hamster with acute WE infection. Arrows indicate examples of LCMV antigen presence in Kupffer cells (1) and in hepatocytes (2). Bar marker represents 100 μm.

Oldstone et al., 1977; Doyle & Oldstone, 1978; Schwartz et al., 1978; Popescu & Ostrow, 1982). In acutely infected hamsters, distinct LCMV-specific immunofluorescent staining in the cytoplasm of what appeared to be mononuclear phagocytic cell types and tissue macrophages was observed. LCMV antigens were also localized in tissue sinuses as aggregates or diffuse debris. Although tissue architecture and cell identification were sub-optimal in acetone-fixed frozen sections, there was usually no clear evidence for the extensive presence of LCMV antigens in organ parenchymal cells. By direct immunofluorescence, LCMV antigens could not be found in neurons, endothelial cells or lymphoid cells. LCMV immunofluorescent staining of liver tissue from a hamster acutely infected with WE is shown in Fig. 5; LCMV antigens were usually found in Kupffer cells and were present in some of the hepatocytes. LCMV antigens were readily demonstrable also in the meninges of the brain, within kidney tubules, and among adrenal gland cortical cells (not shown).

The description, thus far, of lethal and non-lethal LCMV infections in the inbred hamsters is relevant to our understanding of host–virus interactions in arenavirus pathogenesis. The clinical outcome of infection by different arenaviruses in man, non-human primates and selected rodent species may often be related to a balance between systemic infective burden and immunological host control of viral propagation (Peters, 1984; Peters et al., 1987). As presented for the hamsters that were susceptible to lethal disease by WE (Fig. 1, 4), and in a previous study documenting fatal LCMV infections of hamster neonates (Parker et al., 1976), disease and death ensued in hosts with relatively high systemic virus titres. Hamster resistance to and survival from acute LCMV infection was, in contrast, characterized by relatively limited viral growth and by the elimination of virus (Fig. 2 to 4, Table 1; Parker et al., 1976). Similar virological correlations with lethal disease prognosis can also be gleaned from a number of existing reports on primate and rodent arenavirus infections that resemble the haemorrhagic fever syndromes of man.
Fig. 6. Liver section from a hamster after acute WE infection. Note the lymphoplasmacytic infiltrates in the hepatoporal area adjacent to the portal blood vessel. H&E stain. Bar marker represents 100 μm.


In many lethal arenavirus infections, illness and death may be associated with depressed or ineffective antiviral immune responses (Peters et al., 1987). The host immune response has been shown in experimental arenavirus infections to affect disease resistance and survival. In inbred hamsters infected with either LCMV (Genovesi & Peters, 1987b) or Pichinde virus (Buchmeier & Rawls, 1977), and in guinea-pigs infected with either LCMV (Riviere et al., 1985) or selected Junin virus strains (Kenyon et al., 1985), treatment with immunosuppressive agents predisposed the animals to more extensive viral growth and increased clinical disease and mortality. Since there was no temporal impairment in the serum antibody response to LCMV of susceptible inbred hamsters with lethal WE infection and infective virus titres were appreciably reduced after 14 days p.i. in these seropositive animals, we could not attribute the intrinsic susceptibility or resistance to lethal disease to any differences in the humoral immune response to LCMV. Hamster susceptibility or resistance to virulent infection by WE could reflect strain differences in the generation of protective cell-mediated immune responsiveness to LCMV. Cell-mediated immune responses have been documented in hamsters with inapparent, non-fatal, arenavirus infections (Zinkernagel et al., 1978; Nelles & Streilein, 1980; Gee et al., 1981).

Histopathology of lethal and non-lethal LCMV infections in inbred hamsters

In an attempt to understand further the striking differences in the lethality of WE for the different hamster strains, organs of sacrificed inbred hamsters taken during and after acute infection by WE or ARM, were examined in routine H&E tissue sections (Fig. 6 to 8). Generally, the tissue changes in all the LCMV-infected hamsters were minimal and did not include any signs of necrosis. Regardless of the inbred hamster strain examined, sparse to very mild perivascular infiltrates of mononuclear cells, mostly lymphocytes and macrophages, were
noted during acute WE or ARM infection. Perivascular cellular infiltrates consisting mainly of lymphocytes and plasma cells could also be found in the organs of surviving non-viraemic hamsters. These inflammatory lesions were evident in all organs examined, including liver (Fig. 6), kidneys, urinary bladder, brain, reproductive tract, lungs, adrenal glands and alimentary tract (not shown). These lesions were not extensive, even in the tissues of acutely infected animals, and could only be found in an occasional vascular site. An H&E-stained tissue section from the liver of an LCMV-infected hamster, shown in Fig. 6, exhibits some of the typical features of the inflammatory lesions. In the liver these consistently involved several portal spaces and occupied the connective tissue around the portal venule, hepatic artery, biliary duct and lymphatic vessels. This histological presentation in lethally and non-lethally LCMV-infected hamsters was not found in age- and strain-matched uninoculated control animals.

A similar inflammatory histopathology has been described in adult hamsters with inapparent, non-lethal LCMV infections (Smadel & Wall, 1942; Parker et al., 1976). However, hamster neonates with lethal LCMV infection developed an immune complex disease, and histopathological lesions in these animals included an acute necrotizing panarteritis and glomerulonephritis (Parker et al., 1976). As for the inbred hamsters with acutely lethal or non-lethal LCMV infections and the LCMV survivors, we could not find any histopathological evidence for immunocomplex vasculitis or glomerulonephritis.

As noted by Smadel & Wall (1942), the lymph nodes and spleens of all hamsters acutely infected with WE or ARM and of all LCMV survivors were variably enlarged. The histological demonstration of reactive follicular lymphoid hyperplasia (Fig. 7) was consistent with the increased size of these organs and the humoral responsiveness of the hamsters (Fig. 1 to 3, Table 1).

As thus far described, the tissue changes in LCMV-infected susceptible hamsters were not different from those of disease-resistant animals. However, there were pathological findings in
the ileums of moribund and dead WE-infected lethal disease-susceptible hamsters on necropsy. Segmental ileitis was evident in these lethally infected animals. Histologically these ileal lesions consisted of vascular congestion, minimal interstitial haemorrhage, sparse mononuclear inflammatory cells, hyperplastic crypt epithelium, and crypt epithelial growth extension into the intestinal submucosa and muscle layers (Fig. 8). There was no evidence for the same histopathology in the ileums of WE-infected disease-resistant inbred hamsters or in the ileums of ARM-infected hamsters. Perhaps the segmental hypertrophic ileitis was causally related to the clinical progression of the fatal WE-induced wasting illness in the susceptible hamster strains.

In addition to our reports (Genovesi & Peters, 1987a, b), signs of wasting illness were also mentioned in several earlier studies on hamster LCMV infections (Smadel & Wall, 1942; Parker et al., 1976; Förster & Wachendörfer, 1973; Thacker et al., 1982). Of particular interest were the anecdotal comments by Smadel & Wall (1942) and by Förster & Wachendörfer (1973); each had inoculated hamsters with the WE strain of LCMV and noted some fatalities marked by severe weight loss. Smadel & Wall (1942) elaborated on a 'wet tail' diarrhoea in such animals and dismissed LCMV as the cause; although unconfirmed, these deaths were attributed to the bacterial agent of transmissible ileal hyperplasia (TIH) (Jacoby & Johnson, 1981). The clinical manifestation of 'wet tail' diarrhoea was a common feature in hamsters with progressively fatal wasting disease caused by TIH (Boothe & Cheville, 1967; Jacoby & Johnson, 1981) and in all susceptible inbred hamsters with lethal WE infection (Genovesi & Peters, 1987a). The possible involvement of TIH in lethal WE infection of hamsters, although not categorically ruled out, did not appear likely based on current ileal histopathological findings. In hamster TIH, biphasic segmental ileal changes occurred in which crypt epithelial hyperplasia preceded the onset of
severe pyogranulomatous inflammation and multifocal necrosis (Boothe & Cheville, 1967; Jacoby & Johnson, 1981). These latter inflammatory and necrotic lesions were not evident in the susceptible hamsters with lethal WE infection (Fig. 8).

Further investigation of hamster LCMV infections is warranted to unravel the pathogenetic mechanisms behind the fatal WE-induced wasting disease. This research ought to centre on the significance of the segmental ileal lesions (Fig. 8) in WE-induced disease of the susceptible hamster strains. It is possible that in the hamsters susceptible to lethal disease the spread of infective WE to the intestinal tract (Fig. 4) may have induced the ileitis either by direct infection of critical target cells, or indirectly by compromising a number of host physiological regulatory systems. In murine LCMV infection and other arenavirus infections, endocrine and physicochemical disorders have been noted (Barrett et al., 1986; Klavinskis & Oldstone, 1986). In arenavirus haemorrhagic fevers of man and other primates, extensive imbalances in the physiology and metabolism of the infected host have been considered to be major contributing factors in disease progression, and these would require more study to develop effective therapeutic management schemes (Peters & Johnson, 1984; Peters et al., 1987). Future experimental developments on the study of lethal and non-lethal LCMV infections of inbred hamsters could potentially serve as a good model guide to understanding the pathogenesis and immune and therapeutic control of human arenavirus haemorrhagic fevers.

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