The Contamination of Laboratory Animals with Lymphocytic Choriomeningitis Virus

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CONTAMINATION OF A MONKEY COLONY with the virus of lymphocytic choriomeningitis (LCM) was apparently responsible for its original discovery by Armstrong and Lillie [1] on November 2, 1933 during investigation of the 1933 St Louis encephalitis (SLE) epidemic.[2] Thus, from the beginning of its history, LCM demonstrated its now notorious propensity for inducing airborne laboratory infection. The name lymphocytic choriomeningitis [3] does not describe the naturally occurring disease in mice, since choriomeningitis is rare in such animals and naturally infected mice usually show no symptoms at all. The name applies mainly to the results of intracerebral (IC) inoculation of mice and the meningitic complication of the human disease. LCM virus is a lipoprotein-enveloped RNA virus similar in characteristics to the myxovirus group. Multiple discrete electron-dense bodies within the virion give it a unique appearance, and the identical appearance of this virus and of the Machupo-Tacaribe group [4] and Lassa virus [5,6] shows that LCM virus and these agents constitute a distinct new group of viruses. It has been proposed, on the basis of these and other findings, that they be called the areno viruses.[7] The virus called pseudolymphocytic choriomeningitis [8] appears to have been a strain of ectromelia.[9]

Traub [10] showed that different strains of mice varied in the degree to which they became persistently infected with virus and that different strains of virus varied in pathogenicity. Strains of virus that have been passaged to develop viscerotropic properties readily induce tolerance, whereas those passed in the brain and regarded as neurotropic tend not to induce tolerance but to kill newborn mice.[11] Lethal strains are referred to as aggressive, and nonlethal as docile. Most wild strains of LCM virus are the docile or tolerance-inducing type. In spite of the occurrence of strains of LCM virus of different pathogenicity, no serologically distinct variants have been described, and

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all strains share common complement-fixing (CF) and neutralizing antigens.[12–15] Morphologic studies by Dalton *et al*[16] suggest that LCM virus is a pleomorphic agent varying in size from 50 to greater than 200 mμ. While usually appearing to be spherical, it is often cup-shaped. All the particles were found to contain one to eight or more electron-dense granules that were removed by ribonuclease. The virus particles were formed by budding from the plasma membrane and appeared to have spikes. These findings have been confirmed by Abelson *et al*,[17] who used peroxidase-labeled antivirus sera to locate the virions by light and electron microscopy, and also by Kajima and Majde.[18]

The Disease Complex

LCM-susceptible species include the mouse, rat, guinea pig, and rhesus and macaque monkeys, all of which develop central nervous system (CNS) disease. Acute LCM disease of mice begins 5–7 days after IC or intraperitoneal (IP) inoculation and includes a hunched posture, ruffled fur, blepharitis, and facial edema, and is typically culminated at 6–8 days by convulsions and death. In a convulsion, the mouse exhibits rigid, extended hind limbs, which remain extended briefly after recovery of the forelimbs in nonfatal cases. The convulsions may be induced by twirling the sick mouse by the tail. Intranasal (IN) or subcutaneous (SC) inoculation produces temporary illness in mice, followed by solid immunity. Inoculation by any route causes weight loss in mice; this technic can be used[19] as an end-point method for detecting and titrating strains of low pathogenicity. Shaughnessy and Zichis[20,21] concluded that LCM virus can infect guinea pigs through the normal, apparently intact skin. A papular skin reaction after inunction of the virus was reported in rhesus monkeys.[22] Similar lesions were frequently noted in the late stages of LCM infection in these monkeys; histologic examination of the lesions showed edema of the epithelium. Human volunteers[23] and rabbits[24] inoculated intradermally (ID) with LCM virus also exhibited a local skin reaction. Inoculating LCM virus into the foot pad (FP) of mice was found by Hotchin[25] to cause an unusual response in which animals sustained a mild immunizing infection. On the eighth day after injection, the inoculated FP became swollen, followed by gross edema of the leg, lasting approximately 1 week, after which there was full recovery. The FP effect was shown to require live LCM virus. The response was not neutralized by antivaccinia nor anti-ectromelia serum but was neutralized by anti-LCM serum; it was obtained with many

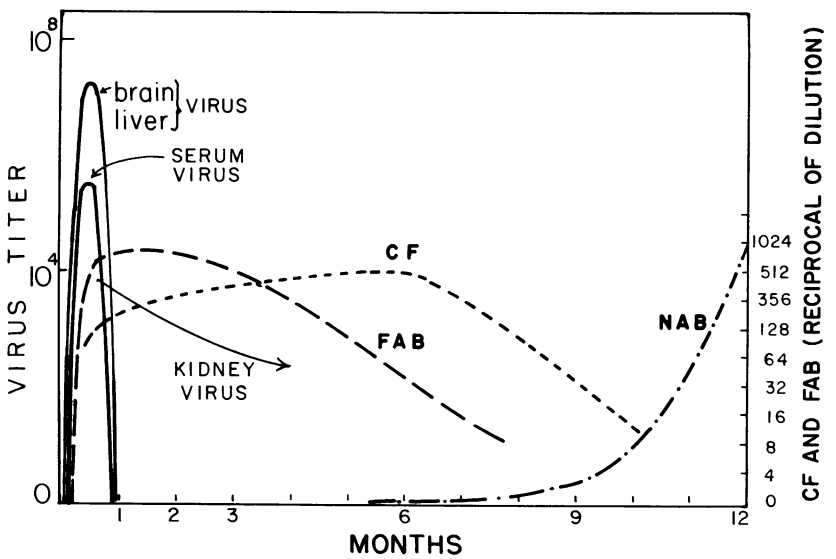
different strains of LCM virus. Histologic study revealed a severe obliterative lesion of the local lymph node during and after the FP response.

LCM virus causes a disease in man,[26] first described by Armstrong and Dickens,[27] ranging in severity from inapparent infection to a rare fatal systemic response. The disease[28] is usually manifested as a mild influenza-like illness sometimes with meningitis,[29] rarely with encephalitis,[30,31] myocarditis,[32] parotitis, orchitis,[33,34] pneumonia,[35] and very rarely as a fatal systematic disease.[29,36–40] Cases with chronic sequelae have been reported that involved fatigue, headache, impairment of memory, mental depression, personality changes [41–45] and, more rarely, meningoencephalitis [43] or paralysis.[46,47] Domestic [48–50] and laboratory infections of man from infected animals are very easily contracted. [38,40,51–57]

Serology

Complement-Fixing Antibody

The main immunologic findings in acute murine LCM are shown in Text-fig 1. Soluble complement-fixing (CF) antigen, which is widely distributed in tissues of LCM virus-infected guinea pigs, mice,[58] monkeys,[59] and chick embryos,[60] is separable by centrifugation from the virus, which fixes complement poorly.[61] It was found to be stable at +4



TEXT-FIG 1—Levels of virus and antibody in acute murine LCM. *CF*, complement-fixing antibody; *FAB*, fluorescent antibody; *NAB*, neutralizing antibody.

C [62]; it was apparently of protein nature and gave a specific CF [63] and precipitin reaction with immune serum.[64] CF antibody to this antigen appears early in the disease of man; experimental animals [59,65–70] have shown that CF antibody appears 1 week after vaccination of mice with live LCM virus and that this antibody is of the 7S (IgG) type.

Neutralizing Antibody

Many workers [64,68,71–75] have found neutralizing antibody to be consistently absent from the sera of LCM immune mice although it has been readily found in other animal species,[54,72,73,75,76] including man.[77,78] Nonspecific, heat-labile,[79] accessory neutralizing factors have also been described [80] in human sera. Neutralizing antibody was tested by Benda [81] for ability to protect guinea pigs against LCM virus challenge after IN administration but only minimal protection occurred. The inability to find LCM-neutralizing antibody in immune mice led some workers [82] to conclude that LCM virus could not be inactivated by antibody at all. More recently, Hotchin *et al* [83] found LCM to be similar to other viruses in respect to susceptibility to neutralization. Salt-free albumin solution was used as diluent, based on observations by Barlow and Weiland,[84] and the animals were inoculated in the FP. A mouse that had recovered from LCM 20 months previously had a high titer (1/625) of neutralizing antibody in the serum. From this and similar results, it was concluded that mice are fully capable of making high-titer neutralizing antibody to LCM virus, but only after a delay of 10–12 months.

Fluorescent Antibody

The direct and indirect immunofluorescent technic has been applied to LCM-infected tissue; the antibody that reacts in this test with LCM antigen is referred to as FAB. Benson and Hotchin [85] developed a quantitative method showing that adult mice produced high levels of detectable FAB, beginning on the sixth day after inoculation and rising rapidly to titers of 1/64 to 1/128 before death by day 10. The FAB was found to be a separate entity from both CF and neutralizing antibody.[15,86] Fluorescent antibody does not protect against death nor neutralize blood virus at all. Complement-fixing,[87] but not neutralizing,[88] antibody to LCM has been found in man during surveys where no human disease was reported,[89] but where there was an association with persistent murine infection.

Histopathology

The major histologic changes in mice after IC or IP inoculation with LCM virus consist of lymphocytic infiltration of the viscera [90,91] and

meningoencephalitis and hepatitis on the fifth day, with a peak in severity on the seventh day.[92] The detailed pathologic histology of murine LCM has been excellently summarized by Lillie and Armstrong [93] and consists essentially of lymphocytic infiltration of virtually the entire animal. Lesions are most severe in the liver and kidneys and vary somewhat in severity with different strains. Neurologic changes are relatively mild, even with neurotropic strains, and consist of meningitic infiltration and sometimes mild encephalitis. Affected animals show marked cellular infiltration of the viscera, with lymphocytes being found especially in liver, suprarenals, kidneys, lungs and meninges.[94–97] High titers of virus are found in all organs.[98] LCM virus in the blood was found by Shwartzman [99,100] to be closely associated with erythrocytes. Remezov and Topleninova [101] showed that immunofluorescence could be used to detect LCM antigen in infected cells and Wilsnack and Rowe [12] concluded that LCM infection in the brain is almost completely restricted to meninges, choroid plexus and ependyma, with little or no multiplication of the virus in brain parenchyma. Evidence of antigen formation began to be found 24 hours after IC inoculation and was extensive by the second day. After viscerotropic virus inoculation, antigen appeared in the lung, bronchial epithelium, alveolar cells and occasional macrophages. The liver was the most consistently infected organ, as judged by immunofluorescence, and was the best sentinel organ for the detection of LCM virus in the mouse. Antigen was evident in hepatic cells 72 hours after IP inoculation of viscerotropic virus. Ten percent of erythrocytes contained specific fluorescent-staining granules, but antigen could not be seen in lymphocytes, except for rare examples in congenitally infected mice. Similar studies have been made by Benda *et al*,[15] Mims,[102] Mims and Subrahmanyan,[103] and Brown.[104]

The lymphoreticular system of adult mice shows marked changes during acute LCM infection.[105] By the third day after infection with viscerotropic and neurotropic virus, the lesions, consisting of pale areas of reticulum with a relative absence of small lymphocytes, were first observed in the cortex of lymph nodes and in the white pulp of the spleen around the central artery. By the seventh day, destruction of small lymphocytes was prominent in the whole lymph node, with extensive cell debris and phagocytosis; by the tenth day, small lymphocytes were almost entirely absent. The distribution of the lesions corresponded to the areas believed to be occupied by the thymus-dependent lymphocytes (TDL). Cortical thymic lymphocytes were destroyed, beginning on the fifth day, until by the tenth day thymic lymphocytes had almost completely disappeared from the cortex, causing a fourfold de-

crease in thymus weight. During this period, virus titers in these organs increased steeply. As early as 1945, similar lymphoreticular changes were reported for LCM by Lillie and Armstrong [93] and more recently for the MP strain of LCM by Molomut *et al.*[106–108] Lymphoreticular damage has been reported to occur in guinea pigs with LCM[109,110] and severe lymphoid and thymic degeneration was reported in guinea pigs infected with Humphreys' virus, which is believed to be LCM.[111] High titers of LCM virus occur in the lymph nodes of infected monkeys.[98] It seems clear from these results that the earliest lesion due to LCM virus in mice is in the thymus-dependent areas of lymph nodes and spleen.

Persistent Infection of Mice with LCM Virus

The major problem in working with LCM virus arises from its ability to induce persistent murine infection that is maintained indefinitely through successive generations of mice. This situation frequently is responsible for inapparent contamination of mouse colonies with LCM virus. The congenital transmission of LCM in mice was apparently responsible for the discovery of the persistent nature of the virus.[1,71,112] Evidence exists for less prolonged persistence in guinea pigs,[71] Syrian hamsters,[113,114] chicks,[115,115a] rats, and rabbits.[115a,116] Some cases of LCM in man have shown minimal signs of persistence.[29,30,44,45,47,117–123] Burnet and Fenner [124] first drew attention to the possibility that LCM induced immunologic tolerance in the host during intrauterine infection acquired from the mother. This concept was based on Traub's extensive work [3,10,66,71,112,125–129] on the pathogenesis of this virus disease in mice. An extensive study of persistent tolerant infection (PTI) of mice with LCM virus has been made by Hotchin.[130] Litters born to PTI mice were shown to be also PTI. Neonatal inoculation of newborn mice regularly caused transmission of the infection to mothers by contact,[85,131] causing inapparent infection and active immunity. No protective antibody appeared to be transmitted from immune mothers to infants [74] and the latter reacted more severely to LCM infection than did normal controls.[132] However, antibody detectable by the FAB technic is transferred from contact-infected mothers to neonatally inoculated infants.[85] Virus was present in the milk of PTI mothers [132a] and invariably caused infection of normal mice suckled by this type of mother. Titers of virus in congenital PTI mice resembled those found in the brains of adult animals suffering from a lethal infection. Both CF and neutralizing antibodies are absent from the serum of LCM-PTI mice,[68,70,74,75] but persistent, low levels of FAB have been found by Benson and Hotchin.[85] The late onset of disease and glomerulonephritic changes in LCM-PTI

mice described by Hotchin [130] suggested [133] that neonatal LCM tolerance was gradually waning, with development of cellular or humoral immunity.

A histologic study by Mims [102] of congenitally LCM-infected mice, using the FAB method to detect LCM antigen, showed that almost all cells were infected in early embryos, and a very high proportion of cells of virtually all tissue were found to contain LCM antigen for at least 8 months after birth. Antigen was most often seen in the form of fine, fluorescent particles which appeared to be in both the cytoplasm and nucleus. Fluorescence of cells tended to decrease as mice became older. Brain showed faint fluorescence, both in meninges and in brain parenchyma, particularly in Purkinje cells. Infected lymphoid cells were seen in the spleen, lymph nodes and thymus. Mims [102] and Mims and Subrahmanyan [103] noted an almost complete absence of pathologic changes for the first 10 months of age after congenital infection of mice with LCM virus. Mims emphasized that this demonstrated the normal functioning of cells heavily infected with LCM virus, particularly in the cerebellar neurons and retinal cells, which contain large amounts of antigen.

Current work in my laboratory [133a] has shown that LCM virus preparations consist of mixtures of two plaque-type mutants. One of these causes lytic plaques and is lethal to newborn mice. The other type produces turbid plaques and induces persistent infection of both cell cultures and newborn mice. The turbid-plaque type has been found to induce a self-limiting transient infection during which virus production is temporary, followed by shutdown of synthesis of viral antigens. After this, the infected cells remain in a refractory state and are resistant to reinfection with LCM for a time, after which they become fully susceptible again. By this means, persistent infection of both tissue culture and animal hosts with LCM virus is believed to be maintained by cyclic transient infection. Once this situation has been established, the majority of the cells in the population are in the refractory state; a small fraction is transiently infected and liberates virus and a few cells become susceptible to reinfection, thereby maintaining the cycle.

Examples of LCM Virus Interfering with Laboratory Experiments

Numerous examples are on record of the discovery of LCM virus as a contaminant of animal or tissue culture extracts used for experiments. In most cases, the presence of LCM virus altered the experimental results significantly. The virus was originally reported by Armstrong and

Lillie [1] and by Traub [112] to cause latent infection in mice. Since then, LCM virus has been repeatedly found as a contaminant of other systems, including canine distemper,[134,135] mycoplasma,[136] which it potentiates sufficiently to cause murine "rolling disease," rabies virus,[137–139] murine poliovirus,[140] lymphosarcoma,[141] Ehrlich carcinoma,[107] and *Toxoplasma gondii*.[142] LCM virus was also isolated from a monkey tissue culture by Coughlin and Whitney.[143]

A remarkable number of examples has been reported in which LCM virus was found to contaminate leukemias.[107,144–152] In several instances, the presence of LCM virus appeared to moderate the severity of the leukemia to a significant degree. LCM virus was found by Hotchin [130] to induce resistance to tumor induction by polyoma virus when it was given to newborn mice a few hours after birth, and polyoma 1 day later. However, LCM infection of L cells did not prevent them from inducing tumors in newborn mice;[153] on the contrary, it appeared to increase the incidence of tumors. Barski and Youn [154] showed a similar interference with the leukemogenic effect of Rauscher virus when LCM virus was given 1 or 2 days previously. Taylor and MacDowell [145] isolated an unidentified viral contaminant of a mouse leukemia that exerted an ameliorative effect upon the leukemia and caused signs of disease in mice that were very similar to those produced by LCM. Law and Dunn [146] isolated a virus, believed to be LCM,[146a] which had an ameliorative effect upon murine leukemia. Experimental infection of guinea pigs with LCM virus significantly increased the survival and decreased the spleen size of animals bearing the transplantable leukemia L2B/N[148] and L2C.[147,152] Stewart and Haas[149] recovered and identified LCM virus in two sublines of leukemia, including L 1210. Humphreys *et al* [144] reported a similar contaminant in the same leukemia strain.

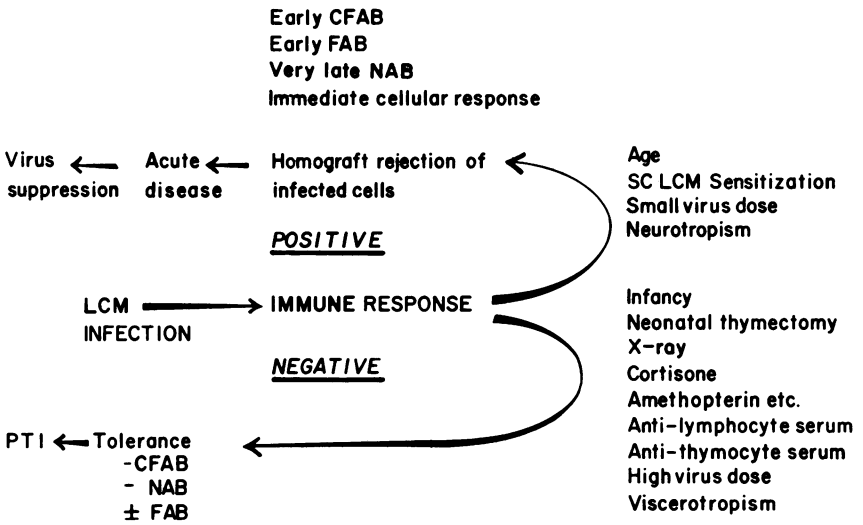
Human infection can result from the contamination of laboratory workers with virus; infection almost invariably will occur after contact with persistently infected animals. In 1935, Traub [112,125] isolated LCM virus from mice that had become sick only after IC inoculation with sterile broth, and also from the blood of the animal caretaker who looked after the LCM virus-infected mice. Laboratory infections appear to be airborne and sentinel guinea pigs show a very high rate of infection if placed in rooms with LCM-infected mice; human infection in such rooms has been observed, and is extremely likely in the absence of appropriate laminar flow systems.[115a] A significant report was made by Lewis *et al* [155] of LCM infection of laboratory personnel that re-

sulted from exposure to inapparently infected hamsters. The infection of the hamsters originated from a spontaneous hamster fibrosarcoma contaminated with LCM virus.

Pathogenic Mechanism

In 1958, it was proposed by Hotchin and Cinits [156] that LCM virus is harmful to the mouse only if the latter responds immunologically to it as a foreign antigen. This concept was later developed [11,74,92,157–159] to a hypothesis that LCM virus is a basically harmless agent capable of inducing a homograft response that causes sickness and death in mice. This explanation of acute murine LCM has been amply confirmed, and the converse situation—the absence of significant immune response by the newborn host—can explain the immunologic tolerance of the mice with persistent infection.[130,157,160] The fact that acute LCM disease and its associated histopathology is completely prevented by immunosuppressive measures (including x-radiation, cortisone, thymectomy, chemical immunosuppressants and anti-lymphoreticular cell sera), provides solid verification for the immune disease concept. The events underlying LCM pathogenesis have therefore been regarded as resulting from one of two alternative pathways of the host immune response being followed, depending on whether this is a positive (active immunity with virus suppression) or a negative (immunologic tolerance or paralysis) response to LCM. These alternative routes are summarized diagrammatically in Text-fig 2. The positive response has two parts, cellular and humoral, which can be separated as "split tolerance" after large doses of virus (HDIP state) and as the tolerance induced by treatment with antilymphocyte or rabbit anti-mouse thymocyte serum, in both of which cellular immunity is impotent but high titers of humoral antibody are found (CF antibody and FAB but not neutralizing antibody).

It has become increasingly evident that the LCM cellular immune response is directed against a virus-induced new or transformed antigen in the surface of the infected cell (see Text-fig 3). A considerable weight of evidence now supports the concept that LCM virus induces the formation of a specific new antigen at the surface of the infected cell. Electron microscopy of LCM-infected cells[16] showed that virus particles are formed at the cell surface by budding, and Abelson *et al* [17] used enzyme-labeled antibody to demonstrate surface LCM antigen. FAB staining of living LCM-infected cells shows the presence of an LCM-induced antigen over most of the cell surface.[160a] The *in vitro* experiments on the immunologically specific cytotoxic reaction between LCM-infected cells and LCM-immune splenocytes, first shown by Ben-



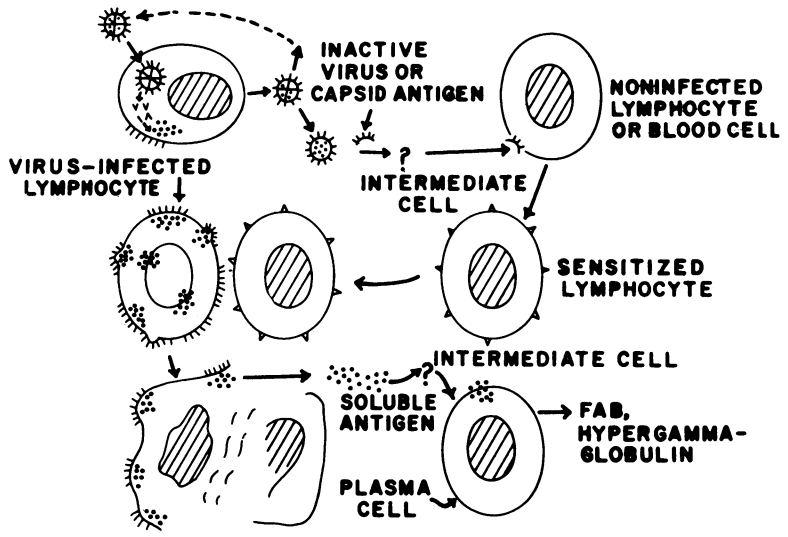
TEXT-FIG 2—The effects of various agents upon the outcome of LCM infection, leading to either immunologic disease or tolerance. *CFAB*, complement-fixing antibody; *FAB*, fluorescent antibody; *NAB*, neutralizing antibody; *SC*, subcutaneous; *PTI*, persistent tolerant infection.

son [161] and confirmed by Lundstedt [162] and Oldstone *et al*,[163] provided additional support for the homograft rejection of acute LCM. Two parameters, virus titer and FAB titer, can be used to classify the three categories of LCM infection.[164] In the neonatal PTI state, cellular immunity is absent, virus titer is high and FAB levels are very low; in the HDIP state, cellular immune response is very slight, so virus titer is high but declines to zero in a period of months; FAB levels remain high. In the suppressive immunity after acute adult infection, both cellular immune activity and FAB are high and virus is eliminated.

Diagnosis

Any mouse dying in the typical convulsive posture of neurotropic LCM should be presumed to have LCM unless further tests refute this diagnosis. However, LCM infection of a colony may not always result spontaneously in such deaths; the virus may be completely tolerated, or may cause nonspecific wasting disease and death, or merely chronic glomerulonephritis. Under these circumstances, proof of infection hinges upon demonstrating the specific antibody, or better, isolating the virus.

A detailed study of the different host responses during titration with mice of LCM was made by Hotchin and Benson,[165] who concluded



TEXT-FIG 3—Diagram of the interaction between cells infected with LCM virus and lymphocytes sensitized to the viral antigen. *FAB*, fluorescent antibody.

that inoculation of the FP was the most sensitive route for virus assay. A titration method for LCM was devised by Lehmann-Grube and Hesse [166] that involved detecting CF antigen released from infected L-cell cultures. However, the method was nine times less sensitive than standard titration with mice. Tissue culture assay combined with direct immunofluorescence has also been described.[167] The simplest definite method of demonstrating the presence of LCM virus is to use the suspected isolate to inoculate groups of 5 or 10 LCM-free mice by the IC route in serial tenfold dilutions. The occurrence of typical convulsions in some of the recipients after 6–10 days is strong evidence of LCM. The diagnosis is readily confirmed by giving the same inocula to mice immunized 2 weeks previously by SC or FP inoculation with a known strain of LCM virus; such mice do not exhibit convulsions or death after IC inoculation with LCM virus. Suspected strains may also be inoculated into mice by the FP route. LCM virus causes enlargement of the affected FP during the following 7–14 days. This response is distinguished from the FP response to ectromelia virus by the absence of rash or necrosis and the subsequent immunity to IC challenge with known LCM virus. In man, the appearance of fluorescent antibody was studied as a diagnostic test by Triandaphilli *et al* [168] and Cohen *et al.*[86] The first antibody to appear after accidental LCM infection was detectable by indirect immunofluorescence using LCM-infected tissue cul-

ture cells; in some cases a significant titer appeared between 1 and 6 days after the onset of meningeal symptoms, declining slowly after several months. In contrast, CF antibody usually appeared considerably later, between 8 days and 2 months after infection; neutralizing antibody was last to show a significant rise, usually after 2 months.

Transmission

The virus is usually transmitted by the airborne route or by contamination of food by infected mouse urine. LCM virus has been experimentally transmitted by various bloodsucking insects,[169] including the Rocky Mountain wood tick (*Dermacentor andersoni*, Stiles),[170] mosquitoes (*Aedes aegypti*),[171] bedbugs (*Cimex lectularius*),[172] fleas,[173] and trinchinella spiralis nematodes,[174] and grows in insect tissue cultures.[175] LCM virus can be regarded as an arthropod-borne virus and it has been suggested [170] that other bloodsucking arthropods such as culicine mosquitoes, stable flies and body lice may transmit LCM from rodent to rodent and possibly to man.

The virus can infect guinea pigs through the normal, apparently intact, skin;[21] guinea pigs and monkeys are particularly sensitive to LCM infection by inhalation.[110,176]

It is also important to realize that LCM virus is capable of behaving as a harmless agent, as well as a lethal one; it produces inapparent disease in chicks,[177] dogs,[178] and in adult rabbits [113] (although retardation of growth is caused in newborn rabbits [179]), newborn [180] and adult Syrian hamsters,[113] and sometimes the mouse.[72] It grows without forming lesions on the chorioallantoic membrane of embryonated hen eggs [181,182] and causes minimal lesions in the embryo,[95] which develops into a normal chick.

Immunization

No satisfactory human LCM vaccine has been prepared and animal vaccination attempts have been relatively unsuccessful. Milzer and Levinson [76,183] were unable to immunize mice or monkeys with suspensions of LCM-infected guinea pig spleen inactivated by heat or formalin. However, these workers claimed to have successfully immunized mice with vaccine of LCM virus inactivated by ultraviolet light. Virus inactivated by oleate or ether was ineffective as a mouse vaccine.[126,128,184] Traub showed that injections of formolized LCM-infected tissue immunized guinea pigs only when homologous tissue was used, and that no parallel existed between immunizing power and virus content prior to formolization. Similar results were obtained by Smadel *et al*,[64]

who showed that soluble antigen was an ineffective immunizing agent, and that, for virus particles to be effective, considerable purity was necessary. Slight protection of guinea pigs against IN challenge with small doses of LCM virus was obtained by SC injection of formolized tissue culture fluid from LCM-infected monkey kidney.[185] Hotchin and Sikora [186] found that heat or 1% formalin-inactivated mouse liver suspension given by SC, IC, or FP inoculation did not protect mice against IC challenge with live LCM virus.

Summary

The literature relevant to contamination of laboratory animals and personnel with lymphocytic choriomeningitis virus (LCM) has been reviewed and summarized. The clinical signs of the disease complex are reviewed for the main species affected, including man. Sections are included on the serology of LCM infections, including complement-fixing, neutralizing and fluorescent antibody, and on the histopathology. Special attention is given to the subject of persistent infection and the pathogenic mechanism of LCM since this is of great importance in the causation of animal and human spread. Methods of diagnosis, transmission and immunization are discussed.

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