SESSION III

EPIDEMIOLOGY AND EPIZOOTIOLOGY

Recent outbreaks of lymphocytic choriomeningitis in the United States of America

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Lymphocytic choriomeningitis (LCM) has been rarely reported in the American literature since 1960. It is interesting that each of the 3 epidemics reported since then has been associated with exposure to hamsters. In 1973, 48 cases of LCM spanning the years 1971–1973 occurred at the University of Rochester Medical School associated with hamsters implanted with tumour tissues. These tissues were found to be LCM-positive, as in an earlier outbreak in 1965 at the National Institutes of Health. A nationwide outbreak of LCM occurred in late 1973 and early 1974 totalling at least 181 cases in 12 states; all were associated with pet hamsters from a single breeder in Birmingham, Alabama. He was an employee of a biological products firm whose tumour tissues were found positive for LCM and were also incriminated in the 1973 Rochester outbreak. The last outbreak occurred in a graduate school laboratory in New York State involving 7 individuals working with hamster tumours from the same Birmingham biological firm. The nationwide epidemic ended in middle April 1974 following removal of incriminated hamsters from pet shops throughout the country and voluntary cessation of distribution of hamsters from the incriminated breeder. The biological firm notified all laboratories of the possible contamination of tumours and has voluntarily stopped distribution of known positive tumours.

Although lymphocytic choriomeningitis (LCM) may be a more frequent central nervous system infection than is generally appreciated in the USA (1, 2), individual cases are apparently uncommonly diagnosed and certainly rarely reported in the American literature. In fact, since 1960 only 6 case reports have appeared (3-8). Also rare have been epidemics of LCM—since 1960 only 3 have been described (9-11). The purpose of this brief review is to summarize the outbreaks of LCM that have occurred in the USA since 1960, with special emphasis on those in 1973 and 1974, and to analyse their possible interrelationships. Of particular interest is the fact that each epidemic and 2 of the 6 case reports have been associated with exposure to hamsters rather than mice, the species previously incriminated as the most important vector in human disease.

In 1965 Lewis (9) and soon afterwards Baum (12) reported an outbreak of 10 cases of confirmed LCM in laboratory personnel working with Syrian hamsters at the National Institutes of Health in Bethesda, Maryland. The remarkable features of this outbreak were (*a*) that it was the first hamster-associated epidemic ever reported and (*b*) that the tumours implanted in these hamsters had been contaminated with the LCM virus. In 1969 Armstrong (6) reported a single case of LCM in a physician who had had limited contact with hamsters in a laboratory that housed LCM-positive hamsters implanted with tumour tissue. The origin of the tumours for both episodes was the same, namely the laboratory of Dr Joseph Fortner at the Sloan-Kettering Institute, New York.

As reported by Hotchin (10) and later by Hinman (13), in the spring of 1973 a series of illnesses occurred in staff members of the University of Rochester Medical Center, which resulted in an intensive investigation and the ultimate discovery of 48 cases of LCM that had occurred between 1971 and mid-1973. Epidemiological and virological investigations incriminated the Syrian hamsters used in tumour research as the source of the virus. There was no evidence that LCM infection had been introduced into the laboratory colony by hamsters

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from outside suppliers; rather, as in Lewis's investigation, the tumour cells themselves were shown to be contaminated. The origin of these tumours was the Southern Research Institute (SRI) in Birmingham, Alabama—a biological firm that has been supplying investigators with a variety of tumour tissues since the late 1950s.

Because the Center for Disease Control (CDC) had assisted in the investigation of the Rochester outbreak and because of our interest in determining whether other tumour cell lines from SRI might be contaminated, an extensive investigation was undertaken at the SRI by Dr Paul Walter, Bureau of Epidemiology, and Dr Vester Lewis, Bureau of Laboratories, in the fall of 1973. Their data, to be published in detail elsewhere, revealed that of 22 hamster tumour lines passed at the SRI between 1959 and 1974, 13 yielded an LCM isolate and that the earliest positive tumour line was passed in 1961. Not only was LCM infection demonstrated in a substantial proportion of tumour tissues, but transmission of LCM from infected hamsters to recently acquired hamsters within the SRI facility was also demonstrated. The original source of virus was not determined.

Coincident with the SRI investigation in early February 1974 came a preliminary report from Monroe County, New York, of 3 possible, apparently unrelated cases of LCM. However, all 3 patients had owned pet hamsters that were subsequently found by the New York State Health Department laboratories to be serologically positive for LCM. Furthermore, although all hamsters had been purchased from different stores in New York State, all had come from a common distributor in Harrison, New Jersey, who obtained his hamsters from a single supplier in Tampa, Florida. Because of the possibility that other hamsters might be infected and spread the disease further, CDC initiated an investigation of the New Jersey distributor and the Florida supplier.

Meanwhile, continuing investigation and surveillance in Upstate New York revealed by late February a total of 6 persons in 2 families in Rochester and a 7th person in Albany with confirmed LCM infection; all 7 had had exposure to pet hamsters in late December. Also, by late February another case of LCM was documented in Reno, Nevada, in a hamster handler who worked at a store supplied by the same supplier in Tampa, Florida. These data strongly suggested that commercial hamsters supplied by this company were contaminated with the virus, and in early March 1974 CDC notified all State and territorial epidemiologists of this discovery and of the possible risk of human infection. CDC urged all State and local health departments to report any suspected cases of LCM to CDC and offered laboratory and epidemiological support for investigations of suspected cases. Furthermore, specific listings of stores serviced by the implicated distributor and supplier were sent to each State to facilitate investigations and case finding.

CDC's investigation of the hamster supplier in Tampa showed that 13 breeders had sent animals to this supplier from 1 December, 1973, through mid-March 1974, and laboratory testing found positive animals in colonies of only 1 of the 13 breeders.

After this breeder had been informed of the results, he voluntarily ceased all hamster breeding and distributed no more hamsters after 18 March, 1974. At the request of State and local health departments, retail stores and pet shops throughout the USA removed from sale all hamsters known to have originated from the Tampa supplier.

The most extraordinary aspect of the entire investigation was that this hamster breeder, whose colony was LCM-positive, was a full-time employee of the SRI who several years previously had started a hamster colony at his home as a supplementary source of income. Although feral rodent contamination of his colony could not be ruled out and although he never stated that the hamsters in his colony originally came from the SRI, the evidence suggests that this, indeed, was the case.

As a result of the nationwide alert and surveillance for LCM cases in humans, a total of 181 cases of laboratory-confirmed LCM infection were uncovered in the period 1 December 1973-April 1974 (Fig. 1). Case-finding methods were directed toward persons with LCM-compatible disease who had had recent contact with commercial hamsters, family members of serologically positive persons, and employees of companies distributing hamsters who had had direct contact with the animals. Cases occurred in 12 different states, with New York and California each reporting 57 cases (Table 1). However, the intensity of case detection varied greatly from State to State, and these figures represent only minimum fractions of all cases. Patients' ages ranged from 2 to 74 years, and males and females were nearly equally affected; 46 patients were hospitalized, but no one died. Clinical and epidemiological features of all these cases will be reported elsewhere by Walter and his associates, but the recent description of the 57

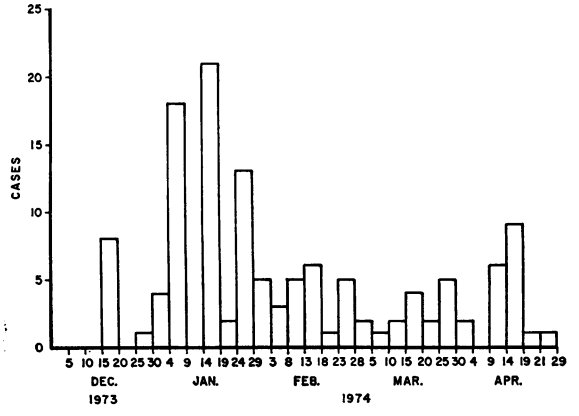

Fig. 1. 127 cases of LCM associated with hamsters, by date of onset, December 1973 to April 1974. The dates of onset for 54 cases are unknown. Reproduced by courtesy of P. D. Walter et al. (unpublished data).

Table 1. Geographic distribution of serologically proven human LCM infection [a]

State	No. of cases
Alabama	16
Arizona	1
California	57
Georgia	5
Illinois	10
Florida	14
Massachusetts	6
Minnesota	1
Nebraska	1
New Hampshire	2
New Jersey	11
New York	57
Total	181

[a] Walter et al., unpublished data.

patients from New York by Biggar et al. is probably a fair representation of the total (14). The earliest reported cases appeared in mid-December 1973 and the latest in mid-April 1974. Most cases were clustered within families, and clinical findings were fairly typical of LCM, with fever, headache, and severe myalgia being the most prominent symptoms. Exposures varied from close intimate handling of hamsters to living or working in the same general area but without direct contact.

The last outbreak of LCM was recognized in October 1974, spanned 14 months, and occurred in 7 of 27 students and faculty of a Cornell University laboratory in Ithaca, New York (15). Clinical illness was typical, and all cases were exposed to tumour-bearing hamsters whose tumour tissue had originated from the SRI and had been introduced into the laboratory in May 1973. No evidence of LCM infection was found, either in the hamsters routinely screened before shipment to the laboratory or in rats used in research and housed in the same room as the positive hamsters.

Although the reports of the 3 laboratory-associated outbreaks referred to above described cases of the disease in some persons who did not have direct contact with hamsters—implying aerosolization as a means of spread—the factors influencing transmission of LCM infection are still not well understood. In general, attack rates are highest in those who have had the most direct intimate contact with infected animals. Yet, individuals indirectly or transiently exposed by the airborne route may also become seriously ill. Furthermore, as reported by Baum, even direct constant contact with infected animals does not always result in clinical disease. In the home setting, as described by Biggar, contact with infected hamsters varied from intimate handling of animals to living or working close to them. Again, severity of illness did not correlate well with the kind of contact; however, attack rates were highest in families where animals were housed in common living areas and in open cages.

In summary, human LCM in the USA over the past 15 years has been primarily associated with exposure to hamsters. Three outbreaks in laboratory personnel were associated with tumour-bearing LCM-positive hamsters, while another, a nationwide epidemic, was associated with commercially sold hamsters supplied by a single breeder and an employee of a biological firm. The Birmingham breeder no longer raises hamsters, and the SRI has voluntarily ceased distribution of positive tumour tissue and has informed all laboratories that have such tissue of the possible risk of LCM infection to their employees. These measures have undoubtedly contributed to the disappearance of LCM infection in the USA since late 1974. However, continued surveillance of commercial hamster colonies and tumour tissues plus investigation of possible feral sources of the virus should be continued to prevent further such outbreaks in the USA.

RÉSUMÉ

FLAMBÉES RÉCENTES DE CHORIO-MÉNINGITE LYMPHOCYTAIRE AUX ÉTATS-UNIS

Aux Etats-Unis, la chorio-méningite lymphocytaire humaine a surtout été associée depuis une quinzaine d'années avec l'exposition aux hamsters. Trois poussées parmi du personnel de laboratoire étaient associées à des hamsters porteurs de tumeurs chez qui on avait isolé le virus de la chorio-méningite lymphocytaire, tandis qu'une autre, de caractère épidémique dans tout le pays, était associée à des hamsters vendus dans le commerce et provenant tous du même éleveur, ainsi qu'à un employé d'une entreprise produisant des substances biologiques. Le fournisseur de Birmingham (Alabama) n'élève plus de hamsters, tandis que le Southern Research Institute a cessé volontairement de distribuer des tissus de tumeurs positifs et a informé tous les laboratoires qui en détiennent que leur personnel risque de contracter la chorio-méningite lymphocytaire. Il n'est pas douteux que ces mesures ont contribué à la disparition de cette infection aux Etats-Unis depuis la fin de 1974. Néanmoins, pour éviter toute nouvelle poussée de ce genre dans le pays, il faudra continuer à surveiller les colonies de hamsters destinés au commerce ainsi que les tissus de tumeurs et étudier toutes les sources possibles du virus chez la faune sauvage.

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DISCUSSION

LEHMANN-GRUBE: Recently, Dr Ackerman in Germany has claimed that LCM infection can cause prenatal disease in babies. The prominent malformation in these reports was hydrocephalus, in two cases associated with chorioretinitis; these newborns also had typical signs of meningitis. The serological evidence in both cases was quite good. There has also been a report, published in *Acta Virologica*, on eight cases of hydrocephalus in the USSR, but the evidence was based only on the presence of immunofluorescent antibody.

K. JOHNSON: I should like to ask those who have worked in the laboratory for years with LCM virus in mice whether they feel that the host-parasite relationship in the hamster is one that more readily leads to human infection than, for example, LCM infection in the carrier mouse.

WELSH: We have some data that may indicate why the virus in hamsters is more infectious to man than the virus in mice. My colleagues and I have looked at the effects of normal human serum on about 20 different viruses. We found that human serum and the complement in human serum without the presence of any demonstrable antibody will directly inactivate many enveloped RNA viruses. When LCM is passed through mouse L-cells, human serum without antibody has a marked ability to inactivate this virus. A 1: 2 dilution of human serum will completely inactivate 100 000 plaque-forming units. LCM virus from L-cells passed once in a human cell line (HeLa) or once in a hamster cell line (BHK) is no longer inactivated by normal human serum unless antibody is present.

LEHMANN-GRUBE: I do not think we should blame the hamster for the severity of the disease. The individual cases that have come from hamsters have all run the usual course of LCM infection—meningitis, sometimes mild, sometimes more severe. The occurrence of severe human LCM infections associated both with *Toxoplasma gondii* and with distemper vaccine suggests that the hamster is not unique in producing LCM strains capable of causing disease outbreaks.

MIMS: I should like to support what Dr Lehmann-Grube has said, but for different reasons. The most important thing is how much virus is shed in the urine and into the environment. It is purely a quantitative matter of how much virus appears in the urine of the hamster carrier.