Lassa fever: review of epidemiology and epizootiology

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The basic ecology of Lassa fever appears to involve enzootic transmission of virus in commensal populations of a single murine species, Mastomys natalensis. *Virus may spill over from the rodent cycle to man by various routes. Secondary spread between humans may occur within domiciliary groups, and persons infected within the community who develop clinical disease may introduce the virus into hospital and begin a cycle of nosocomial infection.*

Between 1969, when Lassa fever was first described, and June 1975, the disease was recognized on 9 discrete occasions, affecting 114 persons. Over one-third of these infections were acquired by person-to-person spread within hospitals. In only one outbreak (in Sierra Leone) were the majority of cases acquired in the community. Recent observations have indicated hyperendemic disease in eastern Sierra Leone. Cases have occurred in Nigeria, Sierra Leone, and Liberia, and serological evidence exists for activity of the virus elsewhere in West and Central Africa. Seasonal factors appear to play a role in the appearance of human cases. Attack rates have been higher in adults than in children. The source of infection and potential routes of virus transmission in the various epidemics are discussed, and perspectives for future epidemiological research are presented.

The outstanding difference between Lassa fever and the other arenavirus diseases is its transmissibility from person to person. The occurrence of sporadic and epidemic nosocomial infections in West Africa and the international transport of persons with the disease have contributed to the current worldwide concern. Epidemiological observations made during the several hospital epidemics of the disease have not provided an understanding of the basic transmission cycle, the dynamics of virus-host relationships, the incidence and geographical distribution of endemic infections and disease, or the various factors accounting for epidemic spread in the community and to the hospital. Partial answers to some of these questions have been provided by the more recent studies in Sierra Leone and Nigeria. In particular, the association of Lassa virus and a primary rodent reservoir-host has been confirmed.

In this report the available epidemiological and epizootiological information on Lassa fever is reviewed and perspectives are given for future investigation and research.

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HISTORICAL PERSPECTIVES

A question frequently asked is whether Lassa fever is a new disease or one of more ancient origin that has been newly recognized. Some insights have been gained by a search of pertinent medical journals for remote published records of clinical entities resembling Lassa fever (Table 1).

Nearly every year during the period from 1920-1950, reference is made in the medical literature on West Africa to the occurrence of cases clinically resembling typhus. Laboratory confirmation was rarely obtained (1), and the features of individual cases are suggestive of Lassa fever (Table 1). Shortly after the recognition of Lassa fever in 1969, Dr Jordi Casals at Yale University brought to light descriptions (2, 3) of a disease in the Oubangi-Chari region of French Equatorial Africa (present-day Central African Republic) and in Upper Volta. Recognized in the late 1930s and called " savanna typhus " by French workers, the disease occurred during the dry season, affected primarily persons engaged in hunting small rodents, and was characterized by a high mortality (approximately 50%), prolonged fever with slow pulse, cardiopulmonary symptoms, severe headache, CNS signs, facial congestion, and terminal hypotension, uraemia, and shock. A rash was

Table 1. Early published records of clinical entities resembling Lassa fever

Year[a]	Reference	Principal clinical features
1935	Cullen, T. *W. Afr. med. J.*, **8**: 15-16 (1935)	Missionary from Makurdi, Nigeria. 14-day history of fever, rash, bradycardia, headache, puffy face. Clinical suspicion of typhus.
1938	LeGac, P. *Bull. Soc. Path. exot.*, **39**: 86-94, 97-103 (1946)	Epidemic disease ("savanna typhus") clinically resembling Lassa fever in Oubangui-Chari. Later studies (Giroud, P. et al. *Bull. Soc. Path. exot.*, **44**: 571-579 (1951)) appear to support a rickettsial etiology (*R. mooseri?*)
1952	Henderson, B. E. et al. *Trans. roy. Soc. trop. Med. Hyg.*, **66**: 409-416 (1972)	Missionary from Rahama, Nigeria. Severe prolonged febrile illness; hearing deficit. Lassa antibody detected in 1970.
1955-1956	Rose, J.R. *Lancet*, **2**: 197 (1956); **2**: 914-916 (1957)	Epidemic in Eastern Province, Sierra Leone, clinically and epidemiologically consistent with Lassa fever.

[a] Year of occurrence of epidemic or case.

noted in Caucasian patients. A rickettsial etiology was suspected. Certain clinical features (in particular the appearance of localizing neurological signs in some cases, the presence of leukocytosis early in the infection, and the absence of gastrointestinal symptoms) as well as the apparently high attack rate during seasonal outbreaks would be difficult to reconcile with a retrospective diagnosis of Lassa fever. Later studies by Giroud et al. (4) suggest that murine typhus was responsible.

Easmon (5) described in detail the medical services, diseases, and conditions encountered in southeastern Sierra Leone in the early 1920s. No unusual sporadic or epidemic illness resembling Lassa fever is mentioned. Recently, however, Dr James Porterfield has called attention to two papers published in 1956 and 1957 by Rose (6, 7), who described an epidemic that occurred between October 1955 and October 1956 in Segbwema, Sierra Leone (very near the 1970-1972 Lassa epidemic site). Forty-five cases were recorded, with a case-fatality rate of 29%; 12 persons, including nursing staff, acquired the disease in the hospital. Clinically, the disease strongly resembled Lassa fever, although CNS signs were more prominent than in recent outbreaks.

In 1971, Henderson et al. (8) reported Lassa-neutralizing antibody in a missionary from Nigeria who had recovered from a Lassa-like illness in 1952.

On the basis of these clinical accounts and seroepidemiological studies, it is probable that Lassa fever occurred without nosological recognition years before the first confirmed case in 1969. Emergence of the disease as a public health problem is due to multiple factors, including: (*a*) improved and expanded health services in endemic regions, (*b*) the use of antibiotics to treat conditions (typhus, typhoid) clinically difficult to differentiate from Lassa fever, and (*c*) the increased numbers of rodent hosts living in association with man, in consequence of the growth of the human population, the clearing of primary forests, and agricultural developments (especially rice cultivation) that provide increased food supply for rodents.

EPIDEMIOLOGICAL CYCLE

The basic ecology of Lassa fever appears to involve enzootic transmission of virus in commensal populations of a single murine species (*Mastomys natalensis*) (Fig. 1). Virus may spill over from these rodents to man by various routes discussed in more detail below. Secondary transmission between persons may occur, especially within domiciliary groups with close contacts or common environmental exposure. Persons infected within the community who develop clinical disease may also introduce the virus into the hospital and begin a cycle of nosocomial infection.

DETECTION OF RESERVOIR HOST

Lassa fever apparently causes overt disease only in man, since the occurrence of human disease has not been associated with die-offs or illness in animal species. The search for a vertebrate reservoir host has focused upon rodents and bats by analogy with the maintenance cycles of other arenaviruses. With the exception of field studies undertaken by the Virus Research Laboratory, Ibadan, in 1972, all

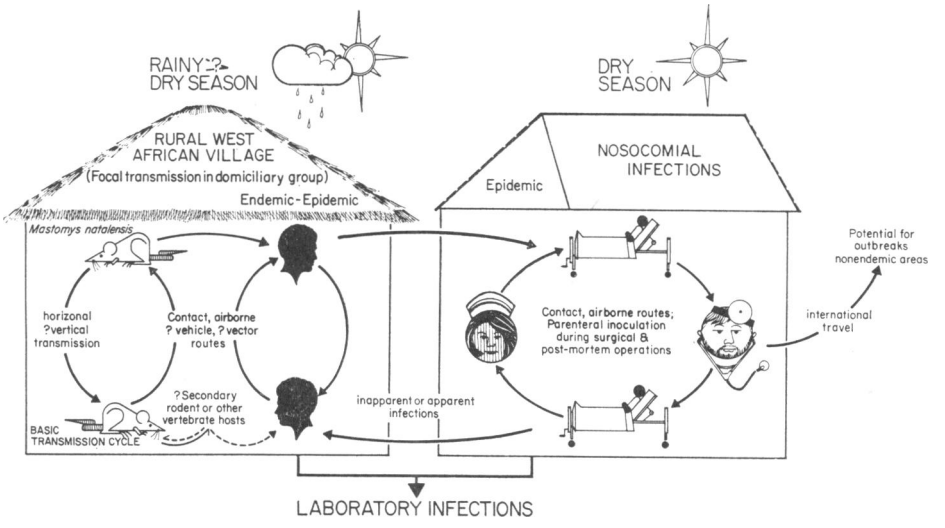

Fig. 1. Diagrammatic presentation of the epidemiological cycles of Lassa virus transmission.

attempts to isolate Lassa virus from animals have been made during or shortly after human epidemics. No virus was isolated during studies in Nigeria in 1970 (9) and in Liberia in 1972, which is not surprising in view of the nosocomial origin of most cases (Table 2).

Table 2. Recorded occurrence of Lassa fever, 1969-1975

Time	Place	Vegetational zones	Season	No. cases	Attack rate	Case fatality (%)	Pattern and presumed mode(s) of transmission	Reference
Jan.-Feb., 1969	Lassa and Jos, Nigeria	Sudan and Northern guinea savanna	Dry	3	—	67	Nosocomial; person-to-person; ? parenteral inoculation (1 case); intimate direct contact	Frame et al. (16)
June 1969	New Haven, CO, USA	—	—	1	—	0	Laboratory infection	Leifer et al. (19)
Nov.-Dec., 1969	New Haven, CO., USA	—	—	1	—	100	Laboratory infection	CDC (24)
Jan.-Feb., 1970	Jos & Vom, Nigeria	Northern guinea savanna	Dry	28	Not determined	54	Nosocomial & intrafamilial person-to-person, direct contact or airborne; parenteral inoculation (1 case)	Carey et al. (9)
Oct. 1970-Oct. 1972	Panguma & Tongo, Sierra Leone	Rain forest	Epidemic peak in rainy season	63	2.2/1000	38	Intravillage and intrafamilial rodent-to-man and person-to-person; nosocomial	Fraser et al. (12) & Woodruff et al. (25)
Mar.-Apr. 1972	Zorzor, Liberia	Rain forest	Dry	11	See text	36	Nosocomial; intimate direct contact; other?	Monath et al. (13)
Jan.-Feb., 1974	Onitsha, Nigeria	Transitional; rain forest/ savanna	Dry	3	—	33	Nosocomial; person-to-person, intimate direct contact	Smith (18), and Bowen et al.(15)
Jan., 1975	Zonkwa, Nigeria	Northern guinea savanna	Dry	1	—	100	Nosocomial; ? parenteral inoculation	A. Woodruff & D. Newberry, personal communication
Jan., 1975	Vom, Nigeria	Northern guinea savanna	Dry	3	—	?	Nosocomial	Frame (14)

Table 3. Results of Lassa virus serological tests and virus isolation attempts on rodent and insectivore specimens captured in West Africa

Time/place	Species	Test employed	No. positive/ No. tested	Reference
1966/Northern Nigerai	Rodents	Ser. PRNT [a]	0/48	Carey et al. (9)
	Atelerix sp.	Ser. PRNT [a]	0/2	
1970/Jos, Nigeria	*Mus musculus* *Mus menutoides* *Rattus rattus* *Mastomys natalensis* *Crocidura sp.*	Vir-Pl [b]	0/39	Carey et al. (9)
1972/Zigida,[c] Liberia	*R. rattus*	Vir-Pl [b]	0/28	Monath & Gary unpublished
	Cricetomys emini		0/7	
	Mastomys erythroleucus		0/4	
	Leggada musculoides		0/2	
	Lophoromys sikapusi		0/2	
	Crocidura sp.		0/1	
1972/Panguma-Tongo, Sierra Leone	*Mus musculus*	Vir-Fl [d]	0/141	Monath et al. (10)
	Mastomys natalensis		14/82	
	R. rattus		0/50	
	Mus musculoides		0/27	
	Lophoromys sikapusi		0/20	
	Other rodent spp.		0/30	
	Crocidura sp.		0/24	
1972/Northern Nigeria	See Wulff & Fabiyi (8)			

[a] Serological test, plaque-reduction neutralization test in Vero cells.
[b] Virus isolation from tissues using plaquing method in Vero cells.
[c] Home village of index case, Zorzor epidemic.
[d] Virus isolation from tissues using fluid cultures of Vero cells.

In September-October of 1972, Lassa virus was first recovered from the tissues of *Mastomys natalensis* rodents during a community epidemic in Sierra Leone (10) (Table 3). Nearly all the virus-positive *Mastomys* were captured in two houses recently occupied by Lassa fever patients. The role of *Mastomys* as a reservoir host has been confirmed by subsequent studies in northern Nigeria (11) during an interepidemic period.

Studies in Sierra Leone indicated that competition for space and food between *Mastomys* and the more aggressive and larger *Rattus rattus* may have determined the distribution and abundance of the host species for Lassa virus (10). Where *Rattus* was prevalent, *Mastomys* tended to give way and the risk of human infection was reduced. It should be pointed out that relatively few rodents of the less abundant species occupying forest habitats have been investigated (Table 3).

Bats have been examined and the results have been negative. Tissues of 31 bats of 6 species collected in Liberia (T. P. Monath, unpublished observations) and of 75 bats (6 species) from Sierra Leone have been tested for virus (10). In addition sera from 20 Liberian bats were seronegative by the complement fixation (CF) test (T. P. Monath, unpublished observations).

No evidence for infection has been found in shrews (*Crocidura* sp.) (9, 10).

Carnivores—in particular dogs and cats, which probably prey upon *Mastomys* and other rodents—have not yet been investigated as potential secondary hosts. If susceptible to infection, they may provide a sensitive serological indicator of enzootic virus activity.

OCCURRENCE

Since Lassa fever was first described in 1969, it has been recognized on nine discrete occasions (Table 2). With the exception of a recent case in Zonkwa, Nigeria (January, 1975), the disease in Africa has been identified only in the setting of an epidemic of 3 or more cases, which emphasizes both the unfamiliarity of physicians with the disease and the inherent difficulties in establishing a clinical diagnosis. A total of 114 cases have been officially recorded, 2 of which resulted from laboratory infections. Over one-third of the cases have been acquired by person-to-person

spread within hospitals. Nosocomial infections have occurred in every outbreak and have predominated except in Sierra Leone. The largest nosocomial epidemic was at Jos, Nigeria, in 1970 (28 cases, of which at least 16 were acquired in the hospital) (9). At Panguma-Tongo, Sierra Leone, a total of 63 cases were reported over a 2-year period (October 1, 1970 to October 1, 1972); 5 of these were believed to be nosocomial, and the remainder were believed to have sources of infection within the affected villages (12).

The continued occurrence of Lassa fever in Sierra Leone has recently been investigated. A review of records at 3 hospitals in the Eastern and Southern Provinces uncovered 211 clinically suspect cases, 18% of them fatal, during the period from October 1, 1972 to June 20, 1975 (K. M. Johnson & T. P. Monath, unpublished observations). Cases were recorded from 67 different localities, indicating widespread endemic virus activity, and only 2 instances of nosocomial infection were found.

The incidence of infection was determined in Sierra Leone for the period October 1, 1970 to October 1, 1972 (12). Cases were recorded from 2 villages with 14 615 inhabitants; the overall attack rate in this population was 2.2 per 1000 (Table 2). Similar attack rates were estimated during 1973–1975 (K. M. Johnson & T. P. Monath, unpublished observations).

Where Lassa fever has occurred as an isolated event involving one or several persons in hospital facilities, it has not been possible or meaningful to define attack rates. During the Zorzor hospital outbreak, however, exposures to the index case took place on a single hospital ward. Seven confirmed cases occurred within a group of 26 exposed hospital staff, giving an " attack rate " of 27% (13).

GEOGRAPHY AND CLIMATE

Laboratory infections excluded, cases recognized since 1969 have occurred in 3 West African countries: Nigeria (38 cases), Sierra Leone (±274 cases), and Liberia (11 cases) (Fig. 2). On the basis of historical information and serological evidence, Lassa fever has also occurred in Telekoro, Republic of Guinea (8) and along the Falémé River in eastern

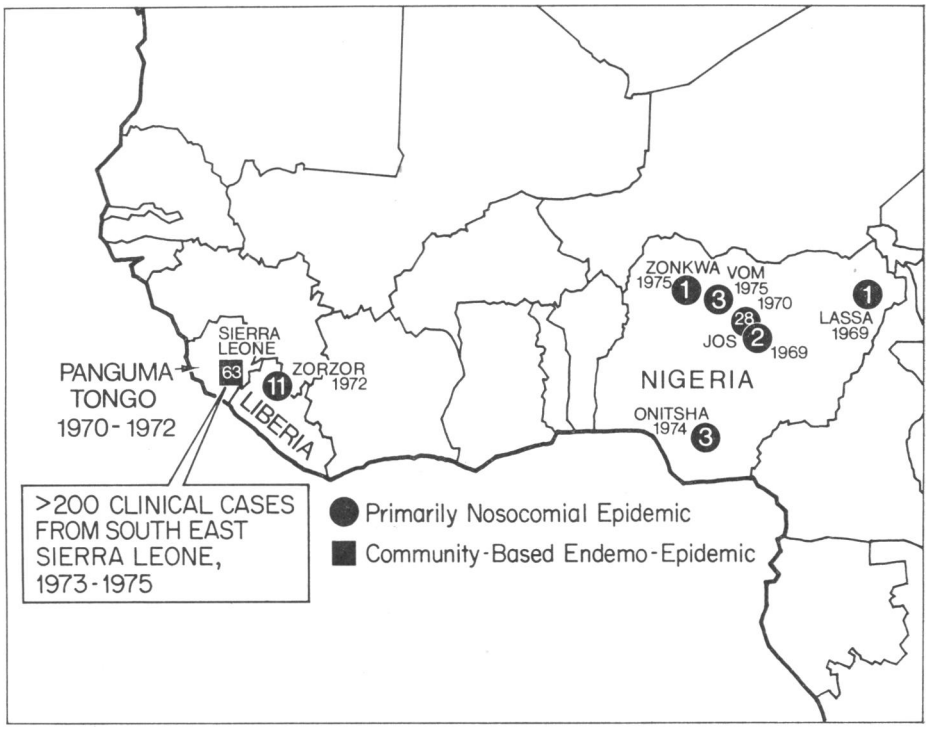

Fig. 2. Locations of Lassa fever epidemics in West Africa and numbers of reported cases.

Senegal (Y. Robin, personal communication). This multifocal pattern of recognized virus activity suggests that a wider dispersion may exist across West Africa and extend into the Central African region (Fig. 2). This possibility has recently been investigated by a serological survey of missionary groups (14), and evidence has been presented for the presence of Lassa virus in Mali and in either the Central African Republic or Zaire (or in both) (14).

The distribution of *Mastomys* throughout sub-Saharan Africa is far wider than that known at the present time for Lassa virus. In some areas Lassa fever may occur without recognition. Possible biological explanations for the discordant distributions include: (*a*) differences in virus susceptibility between subpopulations (genetically and taxonomically distinct) of *Mastomys*, (*b*) the presence of an as yet unidentified primary reservoir host, and (*c*) the presence of other (interfering) arenaviruses.

The endemo-epidemic region in eastern Sierra Leone is characterized by an altitude of 300–600 m, high annual rainfall (250–350 cm), and partially cleared high forest. Rapid expansion of the human population has occurred in this area within the last 20 years, as a consequence of diamond mining activities. The association of mining activities and Lassa fever was noted by Rose in 1955-56 (6, 7), and in 1970-72 the highest prevalence of Lassa virus antibody was found in a mining community (12). The mining areas have in common certain features that may enhance rodent-man contacts, including rapid human settlement, crowding, substandard sanitation, and the emergence of a trading economy with the need to import and store large amounts of rice and other foodstuffs within houses and stores.

The high-rainfall endemic areas of Sierra Leone contrast with the drier open savannas and plateaus affected in northern Nigeria. In Nigeria, serological studies have indicated past infections in northern Guinea savanna and in the savanna woodlands of southern Benue Province (8), but not farther south in the transitional rainforest-savanna region around Onitsha, site of a nosocomial epidemic in 1974 (15).

Nosocomial epidemics have occurred during the dry season. In northern Nigeria cases appeared in January at a time when exposure to wild rodents may be enhanced by hunting activities at the periphery of burning fields. Virus transmission within both the hospital and domiciliary groups by the airborne route may also be facilitated by the relatively high water deficit in the air at this time of year.

The peak incidence of cases recorded between 1970 and 1972 in 2 communities (Panguma and Tongo) in Sierra Leone coincided with the rainy months (12). It was speculated that seasonal shifts in *Mastomys* distribution might have been responsible, with increased numbers of *Mastomys* occupying human dwellings during the rainy months (10). More recent observations in Sierra Leone indicate the presence of endemic disease with no definite seasonal pattern. Further studies of the seasonal incidence of human disease and investigation of seasonal changes in the population dynamics, distribution, movements, and habits of *Mastomys* are required.

MICROCLIMATE

The open construction of the African village dwelling, the general low level of sanitation, and the practice of unprotected grain storage within houses all contribute to large populations of commensal rodents and to enhanced rodent-man contacts.

In a survey conducted in Sierra Leone, Fraser et al. (12) showed that the average number of persons occupying case compounds in Panguma and Tongo was greater than in control compounds in the 2 towns. The CF-antibody prevalence was significantly higher in crowded compounds than in non-crowded ones. Crowding and rodent population density, rodent-man contacts, and person-to-person virus transmission are interrelated.

Environmental conditions within West African hospitals also partially account for the observed epidemiological patterns. Nosocomial outbreaks at Jos (1970) and Zorzor occurred on large, open wards, with closely juxtaposed beds (9, 13). In the Jos epidemic, airborne spread was suspected and may have been facilitated by a prevailing breeze which carried across the bed of the index case to the rest of the open ward (9).

AGE AND SEX

The distribution of cases in nosocomial outbreaks has been determined by the specialized age and sex structure of the exposed population groups.

Observations in the 1970 Jos outbreak (9) and the occurrence of antibody without a history of illness in the child of a missionary from Telekoro, Guinea (8), have suggested that children may have milder infections than adults.

In Sierra Leone, where the great majority of cases were acquired outside the hospital, the incidence of Lassa fever from 1970 to 1972 was highest in adults

Table 4. Age-specific attack rates and CF antibody prevalence Panguma-Tongo, Sierra Leone, 1970-1972

Age (years)	Attack rate (per 1000) 1970-1972	CF antibody prevalence, 1972 (%)
0–9	1.0	5.0
10–19	1.0	5.8
20–29	5.7	10.0
30–39	2.3	2.9
40+	1.0	10.0
Totals	2.2	6.2

aged 20–39 years (Table 4). Young persons 0–19 years of age had a lower incidence of clinical disease, which was not explained by a lower rate of infection as detected by the CF test (Table 4). The difficulty in clinical recognition of the disease in childhood probably accounted for the lower observed attack rate. Case-fatality ratios by age group among hospitalized patients were not significantly different.

The incidence of Lassa fever in Sierra Leone in 1970-1972 was higher in females than in males, and was significantly higher in young adult females (12). In contrast, CF antibody prevalence was higher in males. This discrepancy was in part explained by the fact that Panguma Hospital was used more frequently by adult females than by males. No sex differences in case-fatality ratios have been noted in Jos (1970), Sierra Leone, or in the accumulated hospital cases (Table 5).

Table 5. Lassa fever case-fatality rates by age and sex; hospitalized patients in all epidemics.

Age (years)	Cases (deaths)			Case-fatality rate (%)		
	M	F	Total	M	F	Total
0–9	7 (3)	7 (0)	14 (3)	43	0	21
10–19	5 (2)	4 (2)	9 (4)	40	50	44
20–29	10 (4)	30 (12)	40 (16)	40	40	40
30–39	13 (3)	15 (9)	28 (12)	23	60	43
40–49	5 (4)	5 (4)	10 (8)	80	80	80
50 +	2 (1)	2 (1)	4 (2)	50	50	50
Unspecified adult	2 (1)	—	2 (1)	50	—	50
Totals	44 (18)	63 (28)	107[a] (46)	41	44	43

[a] 4 cases from Jos, 1970, and 3 cases from Vom, 1975, excluded (age/sex data unavailable).

RACE

Both whites and blacks have been affected. Infection of white medical missionary personnel has led to the international movement of Lassa fever cases and importation into America and Europe. The national and international movements of expatriate patients with Lassa fever are illustrated in Fig. 3.

The clinical features in races are similar, although rash has been more often noted in whites. A meaningful comparison of attack rates by race is not possible; however, among hospitalized patients, the case-fatality ratio in whites with Lassa fever has been higher (64%) than in Africans (41%). Although a racial difference in susceptibility is possible, the dose and route of infection and perhaps other variables must be considered. Infection was believed to have been acquired by parenteral inoculation in 4 of 7 fatal cases in whites but in none of the African cases.

OCCUPATION

Medical personnel involved in direct patient care, surgery, pathology, and laboratory testing of clinical specimens have a high risk of infection.

OTHER HOST FACTORS

Background immunity to Lassa virus is probably unimportant in determining patterns of epidemic spread, since the prevalence of CF or neutralizing (N) antibody is under 10% in native populations and only slightly higher in high-risk groups (hospital personnel) (see *Serological epidemiology* below). The possibility that other arenaviruses, particularly lymphocytic choriomeningitis (LCM), may cause human infections in West Africa and alter the clinical or epidemiological expression of Lassa fever has not been investigated.

Persons with unrelated acute or chronic debilitating disease or with compromised immunological responses might be expected to have diminished resistance to infection with Lassa virus; no observations are at present available to confirm or refute this generalization.

Pregnancy does appear to have an adverse influence on the course of Lassa fever (12, 13). Twelve instances of Lassa fever in pregnant women have been recorded (3 in Liberia, 1972 and 9 in Sierra

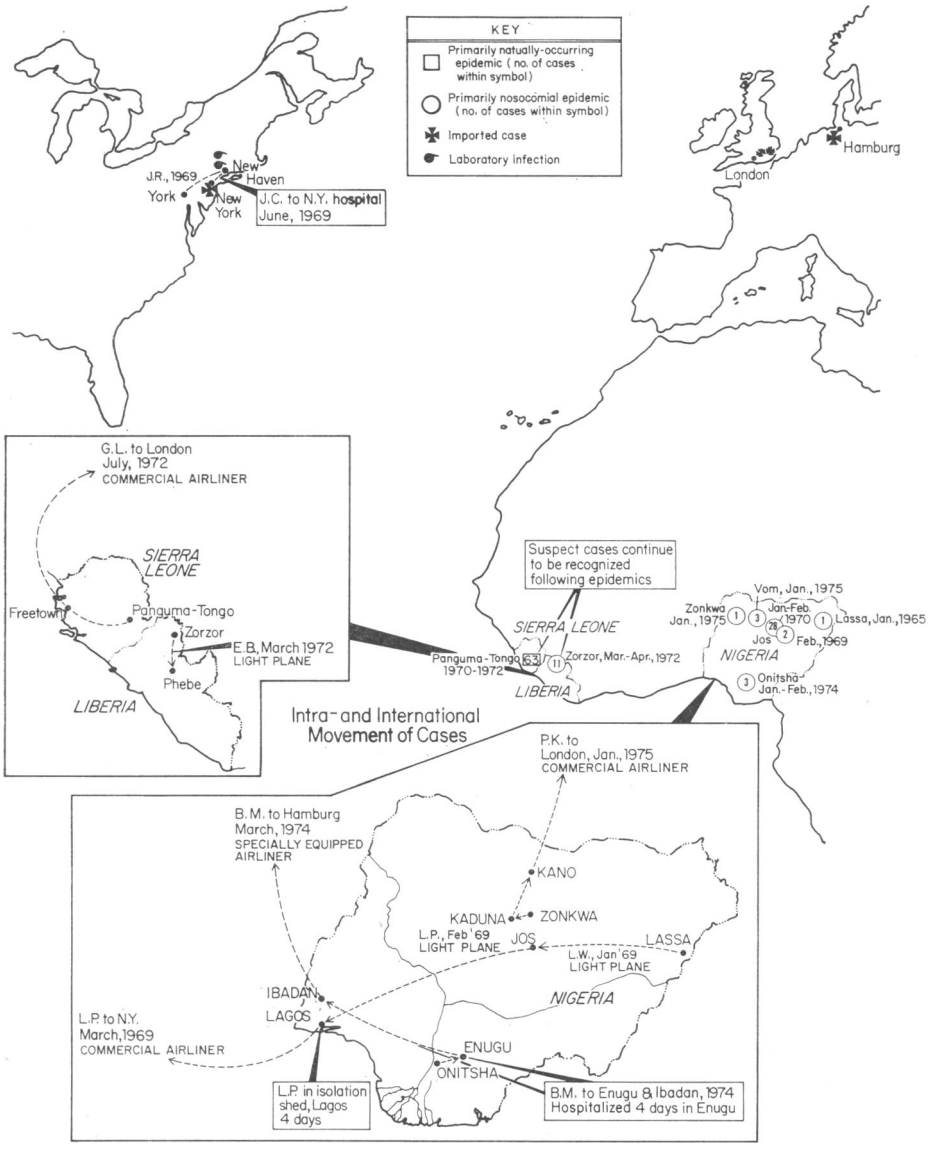

Fig. 3. National and international movements of patients with confirmed Lassa fever, 1969-1975.

Leone, 1970–1972). Eight patients died (67%). Two patients aborted during the illness; in another, fetal heart sounds ceased, and a stillborn infant was delivered during the patient's early convalescence. Observations in Sierra Leone between 1973 and 1975 have also indicated a case-fatality rate in pregnant women nearly double that in non-pregnant women with Lassa fever (K. M. Johnson & T. P. Monath, unpublished observations).

Neither nutritional status nor infestation with protozoan or helminthic parasites appears to be an important host factor in determining the expression or outcome of Lassa fever.

The clinical spectrum of Lassa fever extends from very mild or inapparent to fulminating fatal infection (16–18). The host-specific, epidemiological, and virological factors determining virulence are poorly understood.

SOURCE OF INFECTION

The source of infection in the nosocomial outbreaks has always been a patient admitted to the hospital with an undiagnosed febrile illness, which was later shown to be active Lassa fever. Since a severe transmissible infection was not initially suspected, other hospitalized patients, medical personnel, and visitors were exposed. In all instances, epidemiological review has established the identity of the index case.

Secondary cases in the two large nosocomial outbreaks were apparently not so highly infectious as were the index cases despite the absence of obvious barriers to tertiary transmission. Tertiary infections were, however, documented in a single family group in Jos (1970), in a physician at Jos (1970) and one at Onitsha (18). In the latter two cases, exposures during surgery or postmortem examination were especially heavy.

In Sierra Leone the source(s) of infection for persons acquiring Lassa fever outside the hospital could not be determined with certainty. Both direct infection from the primary rodent source (*Mastomys natalensis*) and infection by secondary person-to-person spread probably occurred. A survey demonstrated clustering of both illness and antibody within domiciliary groups and even within subgroups sharing the same bedroom (12). Since recovery of Lassa virus from *Mastomys* occupying household compounds indicated that virus activity in the rodent host was also quite focal, the epidemiological and serological data were consistent with either rodent-man or person-to-person transmission.

PERSON-TO-PERSON SPREAD

Direct or indirect contact appears to be the route most frequently involved in transmission of Lassa virus from person to person. In the nosocomial outbreaks at Jos in 1969, at Zorzor in 1972, and at Onitsha in 1974, heavy contact exposures were documented. Both direct personal contact and exposure to respiratory droplets occurred while medical personnel were changing dressings and administering mouth care and medication. The virus could have gained entrance to the body via the skin, conjunctivae, or the respiratory or gastrointestinal routes. In Onitsha, a physician may have been infected while performing surgery for relief of tracheal obstruction in a Lassa fever patient; this procedure resulted in a heavy shower of respiratory droplets.

Accidental wounds inflicted by contaminated sharp instruments have caused fatal infections at Jos and Zonkwa, Nigeria. Other instances of indirect contact transmission by linens, bedpans, instruments, or hands are likely but have not been documented.

Airborne dissemination by droplet nuclei possibly accounted for the spread of infection from the index case in Jos (1970) to cohospitalized patients and hospital visitors (9). Both in this outbreak and in the Zorzor outbreak, a number of the secondary cases had no direct contact with the index case, nor were they close enough to the index case for droplet spread to have occurred. Both the prominent respiratory signs in the 1970 index case in Jos and the pattern of air circulation in the affected hospital ward favoured a hypothesis of airborne transmission (9).

Person-to-person transmission by contaminated vehicles such as food, water, intravenous solutions, or medications remains a theoretical possibility. One patient on the affected hospital ward at Zorzor shared food and water with the index case, but probably also had contact exposures. Food and water in African hospitals are generally provided independently by the patient's relatives and the chances of cross-contamination are thereby limited. The vehicle route is more likely to be important within domiciliary groups outside the hospital.

Mechanical transmission of Lassa virus by insects from person-to-person, although a theoretical possibility, does not fit the pattern of spread observed in nosocomial epidemics.

The routes and duration of virus shedding and the concentrations of virus in blood, secreta, and excreta allow some insight into the mode(s) of person-to-person transmission. Lassa virus has been isolated from both the serum and the pharynx 19 days after the onset of illness, and from the urine 32 days after onset (9, 13, 19, 20). The presence of virus in throat washings and the occurrence of symptoms of pharyngitis and pulmonary involvement (cough) in a high proportion of patients support transmission by respiratory droplets, direct and indirect contact with saliva, and the generation of droplet nuclei responsible for airborne spread. The prolonged viruria provides a mechanism for contact and airborne spread and for the contamination of food and water.

The titre of virus detected in the pharynx and urine of Lassa fever patients has been low, varying from trace amounts to 1.75 log $TCID_{50}$/ml (20). Quantitative differences in virus concentration may

explain the observation that only the occasional patient is capable of infecting others.

Serum generally contains somewhat higher virus concentrations than the urine or pharynx [up to 3.4 log plaques/ml (8, 30)]. Viraemias of this magnitude are apparently sufficient to serve as a source of infection by the contamination of sharp instruments and possibly other inanimate objects.

It has not been determined whether persons with subclinical infections or in the incubation period of the disease excrete or are capable of transmitting virus.

Relatively little is known about the resistance of virus outside of the host to heat, radiation, desiccation, and chemical disinfectants. When the virus is present in a protein-rich medium such as blood, casual observations made during transportation and shipment of specimens indicate that the virus is quite thermostable. Heating serum at 56°C for 30 minutes (e.g., in preparation for CF testing) is insufficient to inactivate Lassa virus (H. Wulff, personal communication).

RODENT-MAN TRANSMISSION

The routes of transmission from the rodent host to man can only be surmised, since little epidemiological evidence has been accumulated. Direct contact with infected rodents may occur in rodent-infested households or during active hunting of rodents. Indirect contact with inanimate articles or ingestion of food or water contaminated by rodent urine are possible routes of spread. Airborne transmission or urine droplet contact are more likely modes of spread. *Mastomys* and other rodents clamber over the beams and rafters of huts and houses at night and urine may be dispersed over the room below. In Sierra Leone, room mates tended to have concordant seropositive results and household outbreaks were noted in persons sharing the same bedroom (12).

Recent studies by Walker et al. (21) have demonstrated long-term viruria in colonized *Mastomys* after infection during both the neonatal period and adult life.

RODENT-RODENT TRANSMISSION

The potential routes of spread discussed above also apply generally to horizontal transmission of the virus within rodent populations. The ability of *Mastomys* to develop asymptomatic carrier infections accounts for the high rates of virus recovery observed in circumscribed populations (10). On the basis of preliminary experimental studies (21), it appears that horizontal transmission is possible between adults as well as between adult and neonatal animals. Virus could thus be maintained in a localized *Mastomys* population despite a high prevalence of immunity passively transferred to newborn animals.

By analogy with LCM and Machupo viruses, congenital infection of *Mastomys* may also be a mechanism of importance in the maintenance and focality of virus activity.

Although unlikely, the possibility that Lassa virus may be mechanically or biologically transmitted by ectoparasites of rodents deserves study in the course of future field investigations.

SEROLOGICAL EPIDEMIOLOGY

The serological techniques used include both the CF and the plaque-reduction neutralization test (PRNT). Since CF antibody to Lassa virus is relatively short-lived (1–5 years), this test does not reflect the total accumulated past exposures of the population ground sampled. Moreover, it has been observed that detection of CF antibodies may depend upon the Lassa virus strain used in the test; convalescent sera from Nigerian patients did not fix complement when tested against an antigen prepared from virus isolated in Liberia or Sierra Leone (20). Interpretation of PRNT results is complicated by the repeated difficulty in demonstrating N antibody in the convalescent sera of some confirmed Lassa fever patients as well as in the sera of guinea-pigs hyperimmunized with Lassa virus.

Serological surveys, with the exception of the one carried out in Sierra Leone (12), have not been based on a random sample of the population being studied (Table 6). In surveys of hospital staffs, the bias introduced by selecting individuals at high risk of secondary person-to-person transmission has provided a useful and practical tool for determining Lassa virus activity in a geographic region (12).

The prevalence of CF or PRNT antibody in indigenous West African populations has varied between 2% and 8% (Fig. 4). Serological evidence of past infection has been obtained in Nigeria, Liberia, Sierra Leone, the Republic of Guinea, and Senegal. In another paper to be presented at this Symposium, Frame (14) reports the finding of antibody in sera from missionaries returning from Central Africa and Mali. Sera from missionaries in East Africa have

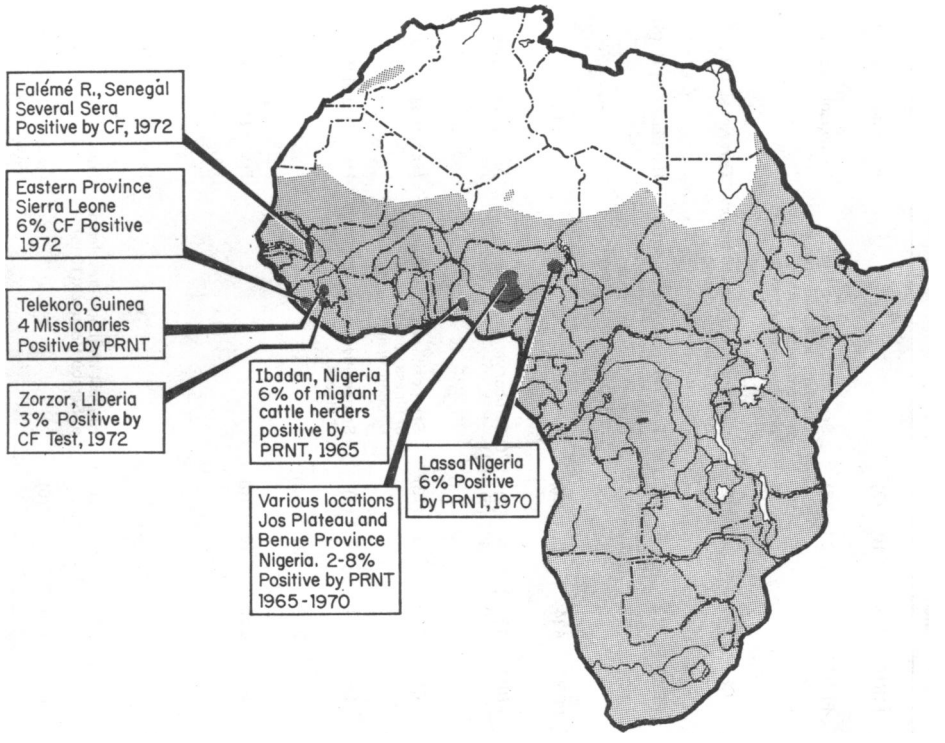

Fig. 4. Summary of serological surveys for Lassa fever antibodies (see also Table **6**) .Shaded area represents the distribution of the rodent reservoir-host *Mastomys natalensis.*

been negative (8), but further surveys of native populations in this area as well as in southern Africa are required.

A 1970 PRNT survey conducted in the area of Lassa, Nigeria, did not show a significant increase in antibody prevalence with age (R. Arnold, unpublished observations). PRNT antibody prevalence in age groups in this sample closely approximated CF seropositivity rates in control households sampled in Sierra Leone (12).

The survey conducted in Sierra Leone demonstrated a significantly ($P < 0.02$) higher seropositivity in members of domiciliary groups that included Lassa fever cases (13% positive) than in control households (6% positive) (12). Similar results were obtained by Arnold (unpublished observations) in Nigeria. In Arnold's study, family contacts of persons found to be seropositive in 1970 were related and compared with a control sample in 1971. Thirteen of 92 contacts (14%) and none of 43 controls were positive ($P < 0.01$), indicating that person-to-person and/or rodent-to-man transmission occurred at a relatively high frequency within household foci.

Seroepidemiological studies have also provided evidence of the occurrence of innapparent or clinically benign Lassa virus infections. In addition to the demonstration of antibody without a history of Lassa fever in survey populations, two instances of asymptomatic serological conversion have been documented among hospital workers (Table 6). In Sierra Leone the attack rate (of hospitalized cases of Lassa fever) was only 0.2% whereas the prevalence of CF antibody in a random village sample was 6% (12). Thus, approximately only one in 30 infections resulted in hospitalization during this outbreak, and the risk of death in persons infected was less than 1 in 60.

PERSPECTIVES FOR THE FUTURE

Lassa fever seems certain to be a perenially important health problem. Underrecognition and underreporting will diminish as clinicians in Africa become more familiar with the disease and as medical facilities expand in rural areas. More important, the

Table 6. Serological surveys for Lassa fever

Time	Place	Population group	Sampling method	Test used [a]	Total No. tested	Total positive No.	(%)	Comment	Reference
1965-1966	Benue Province, Nigeria	Village populations (WHO Treponematosis Survey)	" Selected " sera from original random sample	PRNT	458	10	(2)	—	Henderson et al. (8)
1965-1970	Western & Northern Nigeria	Cattle herders, school children, clinic patients, others	Volunteers, not randomized	PRNT	281	23	(8)	Sera from western Nigeria (Ibadan) collected from migrant cattle herders possibly exposed in the North	Henderson et al. (8)
1970	Jos, Nigeria	Family & hospital contacts of Lassa fever patients	Selected by exposure history during epidemic	CF	172	4	(2)	Seropositives reported history of febrile illness during epidemic period.	Carey et al. (9)
1970	West, Central, & East Africa	Missionaries	Sampled on return from duty	PRNT	712	5 Nigeria 1/257 Guinea 4/17	(0.7)	Four seropositives reported with history of Lassa-like illness; Nigerian case in 1952, Guinea cases in 1965, 1967, 1968	Henderson et al. (8)
1970& 1971	Lassa and neighbouring villages, Nigeria	(a) Villages populations	(a) Sampled all persons attending market day	PRNT	434	25	(6)	See text	Arnold (unpublished)
		(b) Lassa General Hospital personnel	(b) Selected by history of employment during 1969 (first Lassa case discovered)	PRNT	17	0 1	(0) 1970 (6) 1971	Seroconversion in one	Arnold (unpublished)
1972	Zorzor and neighbouring villages, Liberia	(a) Hospital contacts, Lassa fever patients	(a) Selected by history of exposure 3 weeks or more prior to sampling	CF	53	7	(13)	Seropositives gave no history of illness; one asymptomatic seroconversion demonstrated.	Monath et al. (13)
		(b) Inhabitants of index case village	(b) Volunteers, not randomized	CF	144	4	(3)	Seropositives gave no history of illness	Monath et al. (13)
1972	Panguma and Tongo, Sierra Leone	(a) Inhabitants of Lassa fever case households	(a) All household members sampled	CF	206	27	(13)	See text	Fraser et al. (12)
		(b) Inhabitants of control households	(b) Random selection of control households from geographically stratified areas; all household members bled	CF	255	16	(6)		Fraser et al. (12)
		(c) Panguma hospital personnel	—	CF	54	12	(22)		Fraser et al. (12)
1972	Sierra Leone	Hospital personnel	—	CF	133	8	(6)	Highest antibody prevalence at Serabu Hospital (13 %)	Fraser et al. (12)
1972	West Africa	Irish Catholic missionaries several months to 20 years after leaving Africa	Sampled in Ireland	CF	125	0	(0)		Fraser and Monath, unpublished
1974	Onitsha, Nigeria	Case contacts	Selected by history of exposure to Lassa fever cases.	CF	219	0	(0)		G. S. Bowen et al. (15)

[a] All CF and PRNT tests utilized Nigerian strain (Pinneo) of Lassa virus.

growth of human village populations engaged in shifting cultivation in enzootic regions of Africa will provide both for increased densities of commensal rodents and for opportunities for rodent-to-man virus transmission. It also seems reasonable to predict that Lassa virus will continue to be introduced into hospitals serving rural African populations and will spread within these hospitals, as well as to warn of the danger of inadvertent or intentional exportation of Lassa virus to nonendemic areas of the world, in particular Europe and North America.

The geographical distribution of Lassa fever in Africa remains ill-defined; knowledge of it is essential to the establishment of surveillance, to the selection of areas for study of endemic transmission and host relationships, and to the eventual institution of control measures. Preliminary, exploratory surveys for antibody over a wide area would provide much necessary information. For this purpose, gainful use may be made of the high risk of occupational exposure already documented in medical personnel. The advantages of this approach include the practical possibility of obtaining sequential samples from a potentially cooperative and geographically stable population for the determination of incidence data, and the identification of donors of immune plasma.

In areas chosen for study of the endemic disease cycle, more extensive surveys of the general population should be made in order to determine age-specific and sex-specific antibody prevalence data. Well-designed random sampling techniques should be applied. Consideration must be given to the antigenic strain(s) of Lassa virus and to the serological test method(s) used; in addition to Lassa virus, sera should be tested against LCM virus antigen.

Longitudinal studies in an endemic area (such as the Eastern Province of Sierra Leone) will require a multidisciplinary approach. The age-specific incidence and seasonal distribution of human infection and disease in the village and domiciliary group may be determined by sequential antibody studies on randomly selected cohorts and by effective surveillance. Studies of virus activity in the rodent host should be designed to yield meaningful comparisons with the human data. Ecological measurements and determination of virus infection rates should be conducted without removal of animals from study sites. The application of techniques for obtaining urine from live-trapped rodents will be helpful in capture-mark-release studies. Among the important parameters to be investigated are: (*a*) the distribution of *Mastomys* in relationship to competitive species (especially *Rattus rattus*) and the ecological and human factors favouring species dominance; (*b*) movements and migrations, both daily excursions and seasonal and progressive migrations of *Mastomys* and competitive species; (*c*) population density and the dynamics of population as determined by reproduction, mortality, recruitment, and dispersal of young; (*d*) food preference, utilization of various forms of harbourage, and other general habits that may relate to rodent-man contacts; and (*e*) the possibility that infection with Lassa virus may produce pathological lesions affecting life-span or fertility of the rodent host. Methods must be employed for estimating the age of trapped specimens.

In addition, the taxonomic status of *Mastomys* will require careful study. Two morphologically distinct sympatric forms (species) in the Sudan with separate habitats (commensal and wild) have been reported by Setzer (22), and Bellier has presented evidence for two karyotypically, morphologically, and behaviourally distinct subpopulations in the Ivory Coast (23).

Since *Mastomys* does not exclusively inhabit houses, it will be essential to extend trap surveys to fields and forests, both to determine movements of virus and hosts and to exclude a sylvatic transmission cycle involving another species. Surveys conducted in Sierra Leone in 1972 provided insufficient information on the less abundant noncommensal rodent species. Although most arenaviruses are associated with a single host species, some (e.g., Junin) are not.

In addition to field studies, further experimental work is required to clarify the epidemiology of Lassa fever. The susceptibility to infection of *Mastomys* populations from areas within and outside the distribution of Lassa fever should be investigated, as should the sympatric subpopulations with different karyotypes described by Bellier (23). Other species, including *Mus musculus* and *Rattus rattus* should also be experimentally inoculated. The mode of spread from rodent-to-rodent will be elucidated by experiments designed to investigate congenital infection, infection by aerosolized virus, and cross-contamination of cage mates.

In the event of further nosocomial epidemics, epidemiological studies may answer questions about the mode of person-to-person virus spread. Environmental sampling techniques and quantitative assessment of virus excretion will be useful adjuncts to the investigation of the role of the contact and airborne routes.

RÉSUMÉ

FIÈVRE DE LASSA: ÉPIDÉMIOLOGIE ET ÉPIZOOTIOLOGIE

Il ressort de comptes rendus cliniques et d'études séro-épidémiologiques que la fièvre de Lassa sévissait probablement sans avoir été décelée comme telle bien avant que le premier cas ait été confirmé en 1969. La description d'une épidémie dans la province orientale de la Sierra Leone quinze ans avant la flambée de Panguma-Tongo de 1970-72 (3,4) est particulièrement intéressante à cet égard.

Le virus se perpétue dans un cycle où intervient le rongeur *Mastomys natalensis*. L'activité virale paraît centrée dans des populations commensales de rongeurs. Les personnes exposées à ces foyers de maladie dans les habitations peuvent acquérir l'infection directement ou indirectement à partir de *Mastomys*. Il peut aussi se produire une transmission secondaire entre êtres humains, surtout dans une même habitation ou à l'hôpital.

La fièvre de Lassa a été notifiée à neuf reprises. Au total, 114 cas ont été enregistrés, dont deux résultant d'infections en laboratoire. Plus du tiers de ces cas avaient été provoqués par la propagation du virus d'un individu à l'autre dans les hôpitaux. Lors de l'épidémie d'origine naturelle à Panguma-Tongo, Sierra Leone, 63 cas au total ont été confirmés entre 1970 et 1972, dont 58 infections contractées en dehors de l'hôpital. L'incidence de l'infection variait de 27% chez un groupe fermé exposé à un cas initial unique dans une salle d'hôpital de Zorzor, Liberia, à 0,22% lors de l'épidémie dans une collectivité de la Sierra Leone. Il ressort des enquêtes récemment effectuées dans la Sierra Leone que la maladie y est hyperendémique, plus de 200 cas cliniques ayant été observés de 1972 à 1975 dans les provinces de l'est et du sud. Des épidémies ont eu lieu au Nigéria, en Sierra Leone et au Liberia, et des anticorps ont été découverts chez des individus dans d'autres régions d'Afrique occidentale. L'activité du virus semble donc très dispersée et ce fait devra être confirmé par des travaux de surveillance et des enquêtes sérologiques.

Des flambées ont eu lieu dans des hôpitaux pendant la saison sèche, peut-être du fait que le faible degré hygrométrique de l'atmosphère à cette époque de l'année facilite la propagation aérienne d'un individu à l'autre. La répartition saisonnière des infections humaines n'a pas encore été nettement déterminée dans les régions d'endémo-épidémicité.

Les premiers indices donnant à penser que la maladie évolue peut-être d'une façon plus bénigne chez les enfants que chez les adultes devront être confirmés. La littérature fait état d'infections asymptomatiques ou bénignes échappant à toute détection médicale chez des adultes, et elles sont probablement assez fréquentes. On estime que seulement un sujet infecté sur trente est hospitalisé. Le risque d'infection est élevé chez le personnel médical.

Il semble que ce soit par contact que le virus de Lassa est le plus fréquemment transmis d'un individu à l'autre. on a soupçonné une diffusion aérienne lors de deux épidémies nosocomiales, mais le fait n'a pas été démontré. Le virus est présent dans le sérum, l'urine et le pharynx des personnes infectées pendant une longue période.

La maladie peut être transmise de l'urine de rongeur à l'homme par diverses voies, telles que le contact avec des gouttelettes, la contamination des aliments ou de l'eau et la diffusion de fragments de gouttelettes dans l'atmosphère.

Des enquêtes sérologiques ont révélé un taux de prévalence des anticorps de 2 à 8% chez des populations d'Afrique occidentale, le pourcentage de sujets positifs étant plus élevé parmi le personnel hospitalier. Une plus forte séropositivité a été observée chez les contacts familiaux des malades ou des sujets séropositifs que chez les témoins, ce qui indique une transmission fréquente entre individus ou du rongeur à l'homme dans les habitations où il existe un foyer de maladie.

La fièvre de Lassa posera toujours un grave problème du point de vue sanitaire. Des enquêtes sérologiques sont nécessaires pour mieux définir la distribution et les tableaux de l'activité virale, ainsi que des études longitudinales dans une zone d'endémicité pour bien saisir les relations entre le virus et l'hôte et élucider l'écologie et la zoologie fondamentales de *Mastomys*.

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DISCUSSION

FABIYI: Do you have any information on the possibility that Lassa virus is responsible for fetal wastage in pregnant women? From the very limited information we have, it seems that this may be a very common occurrence; women who come in with severe cases of Lassa fever often abort within 4 days of admission.

MONATH: There have been a number of cases of abortion in acute Lassa fever, including the index case at Zorzor and 2 patients studied in Sierra Leone. We do not have any information about teratological effects of the virus.

MIMS: It would be most interesting if we did know that Lassa fever could actually pass the placenta and affect the unborn fetus. I do not think there is any evidence for this at all, because in any severe febrile disease abortion may result, and there are only 3 viruses that regularly pass the human placenta. I have also noticed that hearing defect is quite common in the Lassa fever cases. I wonder whether we might find that deafness actually occurs in every case if one looked for it hard enough. We do not know of many virus infections that affect the inner ear.

FRAME: I have asked the patients I have seen about hearing loss. When questioned directly, about half the people said they had had no discernable hearing problem or any symptom referable to the eighth nerve. The other half had had mild symptoms of one type or another.

EDDY: To judge from the published serological data, the disease seen in Nigeria may be as distinct from that in Sierra Leone as Bolivian haemorrhagic fever is from Argentine haemorrhagic fever; there may, in fact, be two Lassa fevers. In view of this, has any attempt been made to give geographically specific human plasma for treatment of Lassa fever?

MONATH: When convalescent sera from a group of patients from the 3 epidemic areas—Liberia, Sierra Leone, and Nigeria—were tested by complement fixation against viral antigens from those 3 areas, it was noted that serum from patients who had recovered from the disease contracted in Nigeria did not fix complement in the presence of antigen from patients from Sierra Leone or Liberia; these results were reproducible. However, Dr Wulff yesterday showed us results of indirect FA tests

that did not seem to indicate any difference between virus strains from those 3 areas. Clinically, I do not think there are any apparent differences in the disease from the 3 areas. Efforts have been made to collect immune plasma in West Africa, and generally the material has been stored and used in the area where it has been taken. I might add that immune plasma from a Nigerian case was successfully used in the treatment of 2 patients in Sierra Leone.

CASALS: I would add that only when a neutralization test is available will it be possible to answer Dr Eddy's question. Machupo and Junin viruses are almost indistinguishable in the complement fixation test, yet in the neutralization test they show hardly any relationship.

SMITH: As has been pointed out, Lassa fever is not a new disease but an old one that has been diagnosed in recent times. Its epidemiology is not yet fully known because of lack of proper reporting, poor education of medical personnel, and complete absence of knowledge about the disease among some personnel in the very areas where Lassa fever has been recognized. So far Lassa fever has been reported from at least 3 states of the Nigerian federation: the Benue Plateau, North Central State, and East Central State.