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Current Opinion in Virology

A short history of Lassa fever: the first 10–15 years after discovery

Thomas P Monath

This brief review is focused on the events surrounding the initial discovery of a new viral hemorrhagic fever in 1969 and the subsequent 10–15 years during which a substantial understanding of the disease was gained. In 1969, a series of sequential life-threating or fatal infections occurred among health care workers in Nigeria and the laboratory scientist who isolated and characterized the causative agent. The agent, Lassa virus was named after the geographical location of the first recognized human case. The new virus was shown to be related to lymphocytic choriomeningitis and to previously unclassified neotropical viruses, including Argentine and Bolivian hemorrhagic fevers, and a new taxonomic grouping, the Arenaviruses, was proposed. In 1970–72, three further epidemics occurred in Nigeria, Liberia and Sierra Leone, the first two involved nosocomial transmission, and the third was a community-based outbreak, during which the rodent reservoir host was identified. In 1976, a long-term research project commenced in Sierra Leone, which produced a rich body of data from prospectively designed studies on the clinical features, transmission, and treatment of the disease.

Address
Crozet BioPharma LLC, 94 Jackson Road Suite 108, Devens, MA 01434, United States

Corresponding author:
Monath, Thomas P (tom.monath@crozetbiopharma.com)

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Lassa fever was first described in 1969 in Nigeria. Today it is a growing public health problem in West Africa, where 59 million people are at risk and 3 million cases and 67 000 deaths may occur annually [1]. The World Health Organization's Blueprint for Action prioritizes development of a vaccine [2], and the Coalition for Epidemic Preparedness Innovations (CEPI) is funding vaccine development.

Shortly before recognition of Lassa virus, Greer Williams' Virus Hunters chronicled the great discoveries in virology [3]. The future emphasis was identified as chronic viral infections, vaccines against common viral infections, and viruses as a cause of cancer. A different concern soon took shape over 'emerging viruses', spawning a new breed of Virus Hunter [4].

In the 1940s, Soviet workers described hemorrhagic fever with renal syndrome, Crimean (now Crimean-Congo) and Omsk hemorrhagic fevers. In the 1950s, new hemorrhagic fevers were recognized in Thailand (dengue hemorrhagic fever, 1954), India (Kyasanur forest disease, 1957), Argentina (Argentine hemorrhagic fever, 1958) and Bolivia (Bolivian hemorrhagic fever, 1959). In each case, discovery coincided with ecological perturbations, often of human making. Rodents were ultimately implicated as the reservoir host of 5 of the 7 'new' diseases. One important common feature was that none appeared to be transmissible person to person.

In 1967, a new hemorrhagic fever affected 31 laboratory workers in Germany and Yugoslavia, with 7 deaths (22.5%). The outbreak was notable in several respects: a new agent, Marburg virus, unrelated to other known viruses was identified; its origin was infected monkeys transported from Africa by air; it affected western Europe; it had high lethality and dramatic clinical picture; it was acquired through contact with blood and tissues; and there was human–human transmission (including sexually via infectious semen). In response, steps were taken to construct high-containment laboratory facilities. This outbreak foreshadowed and influenced the response to Lassa fever two years later.

Today the names of individuals would be withheld due to privacy concerns. Not so in January 1969 when an American nurse, Laura Wine, at a mission hospital in the remote village of Lassa, northern Nigeria, developed fever, back pain, sore throat with ulcers, leukopenia, swelling of the neck and renal failure. By the time evacuation by road and light plane to Bingham Memorial Hospital in Jos was arranged, she was desperately ill with respiratory distress, petechial rash, hypotension, obtundation, and convulsions. Despite intensive care, she died in 24 hours, 6 days after onset. Gross autopsy showed internal hemorrhages but was otherwise uninformative.

Eight days later, Charlotte Shaw, a nurse who had attended Wine, fell ill. She had an open cut on a finger when she swabbed Wine's throat. Shaw's illness

recapitulated the preceding patient, and she died 11 days after onset. Both Wine and Shaw were treated by Dr Jeannette Troup and nurse Penny Pinneo, and they had performed an autopsy revealing hemorrhage and signs of multi-organ failure. A week after Shaw's death, Penny Pinneo developed fever followed by specific signs seen in Wine and Shaw. Informed by preceding cases, physicians at the Jos hospital, including Dr Hal White, made arrangements for Penny (and samples from Wine and Shaw) to be evacuated to New York, under the care of the Director of Medical Services, Sudan Interior Missions, Dr John Frame. Pinneo's tortuous journey, long delays over access to a commercial flight and quarantine in a decrepit smallpox isolation unit near Lagos, and finally hospitalization at Columbia Presbyterian, have been described in detail by Fuller [5], Garrett [6], and Pinneo herself [7]. Her case initiated considerable debate about international transport of patients with high consequence infections that conflated these events with the previous Marburg incident.

Pinneo had a complicated recovery over nine weeks. Frame *et al.* published the first report, naming the disease Lassa fever after the location of the original case; a virus isolation had been made but defied identification at the time [8]. They concluded:

> "If all three cases were accepted as exemplifying the same disease process, we knew of no African disease that fit the epidemiologic pattern: an acutely ill, aged missionary nurse is flown 200 miles to a mission hospital where she dies; a week later her nurse becomes ill, dying on the 11th day of illness; the head nurse of the hospital who nursed her and who assisted at her autopsy becomes ill in yet another week. Some of the clinical findings suggested virus hemorrhagic fever, apparently not yellow fever, and not reported previously in Africa".

In June 1969, several months after initiating studies at the Yale Arbovirus Research Unit (YARU) with the patients' samples, Jordi Casals (Figure 1), one of the world's most revered arbovirologists [9], developed Lassa fever and was hospitalized at Columbia Presbyterian [10]. Although the source of Casals' laboratory infection was not identified, suspicion fell on mice inoculated with infectious material which did not show illness but shed the virus in urine for weeks, and on homogenization of mouse brains to generate antigens.[1] As a result, Casals and colleagues speculated that rodents may be the source of human infection in nature. Another clue was that baby mice rarely showed signs of illness, while adult mice inoculated intracerebrally developed neurological signs similar to those caused by lymphocytic choriomeningitis virus (LCMV). Five years earlier, Johnson [11] and Webb [12], investigating Bolivian hemorrhagic fever (Machupo) virus, which was unclassified at the time, had suggested similarities to LCMV. This proven to be prophetic. In 1969, Murphy, Webb and colleagues reported that Machupo resembled LCMV (and Tacaribe virus) by electron microscopy and proposed a new taxonomic group [13]. Serological relationships between LCMV and the Tacaribe complex viruses were shown by immunofluorescence and the name Arenavirus proposed after the electron-dense ribosomal granules inside virions [14–16][2]

Figure 1

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Jordi Casals-Ariet, PhD (1911–2004), Rockefeller Foundation virologist who lay many of the foundations in the field of arboviology, and first isolated and characterized Lassa virus. During the early work on the virus at the Yale Arbovirus Research Unit in 1969, he contracted a laboratory infection with Lassa, and was treated with convalescent plasma from Penny Pinneo, the first patient to have survived after acquiring the disease in Nigeria.

At YARU, viruses were isolated from sera of Wine, Shaw, Pinneo and Casals in Vero cells [17], and the Pinneo virus was selected as prototype. Cell lysate antigen reacted with convalescent sera. Titers at passage $Vero_1$ were 2.0–4.5 $TCID_{50}$/mL but reached 7 logs on second passage. A low-level cross-reaction by complement-fixation was found between Lassa and LCM viruses, as well as with Amapari, Junin, and Tacaribe [17]. Lassa virus particles were indistinguishable morphologically from those reported by Speir *et al.* for LCMV, Machupo and Tacaribe [18].

[1] Another laboratory infection occurred at YARU in a technician who was not directly working with the virus, and he tragically succumbed to the disease.

[2] Forty-one viruses including the New World and Old World agents causing viral hemorrhagic fever are now assigned to the family Arenaviridae, genus Mammarenaviruses (Maes P, Alkhovsky S, Bào Y, *et al.* Taxonomy of the family Arenaviridae and the order Bunyavirales: update 2018. Arch. Virol. 2018 doi: https://doi.org/10.1007/s00705-018-3843-5.

Local residents remonstrated that the virus name adversely stigmatized Lassa town. In light of Casals' discovery, the suggestion was made to change the name to 'Cassel's (sic) virus'. This proposition reached the Nigerian Ministry of Health and WHO, to no avail.[3]

In January 1970, shortly after its identification, Lassa virus struck two mission hospitals in Jos, Nigeria. This was another nosocomial outbreak, with 28 cases, 16 acquired in hospital, and 13 deaths (46%). The outbreak was investigated by Don Carey and a team from the Rockefeller Foundation Virus Research Laboratory in Ibadan [19]. The outbreak allowed a more comprehensive description of the clinical features and pathology of the disease [20,21]. Dr Jeannette Troup, who had treated Wine, Shaw and Pinneo, cut her finger while performing an autopsy on an early case, and succumbed to the disease, a familiar theme in the history of viral hemorrhagic fevers. The prominent feature of the epidemic was the spread within one ward of the hospital, where the index case lay in front of a corner window upwind of the rest of the ward. The high attack rate on the ward, cases among visitors, and subsequent transmission of the virus from the index case to relatives after discharge, suggested that she was a 'superspreader', that airborne transmission might be responsible, and that the virus may persist and be transmitted after recovery. Taken together with the Marburg virus incident two years earlier, the contemporary literature filled with concerns about international spread. However, it is now clear that person-to-person transmission of Lassa virus is rare. In most nosocomial outbreaks of Lassa fever, barrier nursing was not used and blood-borne transmission via re-use of needles and surgical instruments was implicated in some instances [22].

My initiation came in March 1972, while I was a CDC research fellow at the Rockefeller lab in Ibadan, Nigeria, and was asked to investigate an outbreak, confirmed as Lassa fever, in Zorzor, Liberia. I was joined by Penny Pinneo (Figure 2), who, being immune, was of great assistance in undertaking high-risk procedures. This was another nosocomial epidemic with 11 cases and 4 deaths (36%). As in Jos, most cases were on one (obstetric) ward, where 7 cases occurred among 26 hospital staff, an attack rate of 27% [23]. A review of hospital records indicated that cases resembling Lassa had occurred in the past. An interesting aspect was identification of the index case, a woman from Zigida, 24 miles north of Zorzor. It was possible to find her house, and to focus collection of rodents and bats. Unfortunately, no virus isolations were made from these animals.

Figure 2

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Penny Pinneo, the first recognized survivor of Lassa fever, and Dr Paul Mertens, physician at Curran Lutheran Hospital who participated in the investigation of the nosocomial epidemic in Zorzor, Liberia, 1972.

In August 1972, Paul Goff, a Peace Corps physician in Sierra Leone alerted CDC to an outbreak in Panguma, Eastern Province. I was asked to stand up a team and was especially keen to discover the natural transmission cycle of the virus. The team included epidemiologists David Fraser and Kent Campbell, Graham Kemp, Vern Newhouse, Penny Pinneo, Jordi Casals and myself. The investigation led to the following conclusions: first, most of the 63 cases identified were community-acquired and

[3] Although new arboviruses and related viruses of vertebrates are typically assigned a name corresponding to geographical origin, avoiding the stigma of association with a severe disease has been useful, *viz.* Ebola virus after a nearby river rather than the town of origin (Yambuku), and Junin (a district) in place of the original O'Higgins disease after the name of the town in Argentina where the initial outbreak was described.

Figure 3

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Top, Drs Graham Kemp (Rockefeller Foundation veterinarian-virologist) and Vern Newhouse (CDC entomologist and arbovirologist) processing mammals collected in Panguma during the 1972 outbreak. Bottom, right, rodents collected before processing; tissue samples were frozen in liquid nitrogen and returned to CDC, Atlanta for virus isolation and carcasses were preserved in formalin for taxonomic identification at the Smithsonian Institute by the Curator of Mammals, Dr Henry Setzer; Bottom left, *Mastomys natalensis*, the reservoir host, identified in the 1972 Panguma outbreak.

had occurred over at least two years, a dramatically different picture than in previous nosocomial outbreaks [24]; second, the rodent host was identified for the first time, the multimammate rat *Mastomys natalensis* [25] (Figure 3); third, the incidence of infection in the community could be estimated (2.2 per 1000); fourth, persons in case households were more often seropositive than in non-case households, indicating transmission hot spots (this would be later confirmed in a case-control study [26]); fifth, inapparent infections were common, with an estimated ratio of asymptomatic to symptomatic cases of 30:1; and finally, simple patient isolation methods abrogated nosocomial spread. The latter was confirmed some years later in a prospective survey of health workers caring for Lassa fever patients using simple barrier nursing that revealed no increased risk of infection over that in the local population [27].

Further outbreaks of Lassa fever occurred in Nigeria and Sierra Leone between 1973–1976 [28,29]. It was clear from these events, serological surveys, and surveillance of missionaries that Lassa virus was widely distributed in West Africa [30,31]. While the rodent host of Lassa was now known, the factors underlying persistent infection and human exposures were poorly understood. The situation was reviewed at an international congress and published in Bull WHO [32].

A long-term research program was needed to investigate Lassa fever and its rodent host in depth rather in

continuing fire-fighting outbreak investigations. Moreover, anecdotal reports of successful treatment of Lassa fever with convalescent plasma [10] required confirmation. In 1975, Karl Johnson and Pat Webb, who had played a critical role in investigating Machupo, were leaving NIAID's Middle America Research Unit in Panama for CDC, Atlanta. In 1975, Karl and I went scouting for a suitable study site in Sierra Leone. A review of hospital records indicated that there was long-term activity of the disease; this was subsequently confirmed [31]. The Eastern Province of Sierra Leone, together with the bordering area of Liberia, has been shown over the years to be at highest risk [33].

In 1976, CDC established the Lassa Fever Project in Kenema, Sierra Leone under the leadership of Dr Joe McCormick (Figure 4) and later moved to Segbwema when Pat Webb [34•] became Director in 1978. The Project is described in McCormick and Fisher-Hoch's book [35]. Using prospective methods, McCormick pursued anecdotal findings from earlier studies. He increased awareness of the disease, improved patient care practices [36], and attempted prevention through medical education and published a rich body work. A notable accomplishment was a randomized clinical trial of convalescent plasma versus oral ribavirin, which suggested that ribavirin treatment in the first week after onset reduced mortality, whereas convalescent plasma, which had been promulgated as an intervention [37], was ineffective.[4] A follow-on study of intravenous ribavirin showed significantly reduced mortality from 55 to 5% [38]. The severity of Lassa fever in pregnancy with poor fetal outcomes was established [39]. The antibody response, viremia and virus shedding were defined, and aspartate transaminase levels >150 IU/L shown to be a prognostic indicator and trigger for ribavirin therapy [40]. Prospective studies documented a ratio of illness to infection of 9–26%, confirming that inapparent infections were common [41]. Deafness, noted in early case reports, occurred in 20% of patients, exceeding other infectious diseases [42].

Figure 4

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Dr Joseph B. McCormick, a CDC physician-epidemiologist, led the long-term research program on Lassa fever in the Eastern Province of Sierra Leone, initiated in 1976 and resulting in a series of prospective clinical and epidemiological studies that underlie much of what is currently known about Lassa fever.

New arenaviruses were discovered in southern Africa. In 1977, a virus serologically related to Lassa was isolated from *M. natalensis* in Mozambique [43] and Zimbabwe [44]. In experimental studies, the virus was non-pathogenic for rhesus macaques but protected against Lassa virus *sensu strictu* [45]. Later designated Mopeia virus, it is a candidate live, attenuated vaccine against Lassa fever [46]. Subsequently, a number of other non-pathogenic arenaviruses have been described in Africa (e.g. Ippy, Morongo, Mobala, Menekre, Gbagroube, Kodoko viruses) as well as Lujo virus causing hemorrhagic fever in a nosocomial outbreak in Johannesburg in 2008 [47]. Undoubtedly the list of Old World arenaviruses will expand.

The studies in Sierra Leone were halted in 1993–2001, during the Blood Diamonds War. Recognizing that many questions about the disease remained unanswered, Tulane University rebuilt the field program in Kenema, supported by laboratories in New Orleans. Key investigators included

[4] The neutralizing antibody level of the plasma units used in this study was not determined. This raises questions about the validity of the conclusions of the study, since the strength of neutralizing antibody in convalescent plasma determines effectiveness in the macaque model (Jahrling JB, Peters CJ, Infect Immun 1984;44:528-533). The late appearance of neutralizing antibodies, possibly due to masking neutralizing epitopes by the virions' glycan shield could have limited the therapeutic activity of convalescent plasma used in McCormick's study. More recently, a cocktail of neutralizing human monoclonal antibodies administered to macaques up to 8 days after Lassa virus challenge when they were clinically ill has been shown to be protective (Mire CA *et al.* Nat Med 2017;23:1146-1149), suggesting that immunotherapy is feasible.

Bob Garry, John Schieffelin, and Dan Bausch. Investigations have centered on pathophysiology of the disease, immunodiagnostics, and cross-cutting work on monoclonals for therapy, vaccines and viral genomics. As this work is ongoing, it falls beyond the scope of this historical overview. Additional partnerships include the Institute of Lassa Fever Research and Control, Irrua, Nigeria collaborating with Stephan Günther's group at the Bernard Nocht Institute of Tropical Medicine, Hamburg. Recently, Lassa virus isolations have been made from *Mastomys erythroleucus* and *Hylomyscus pamfi* in Nigeria, indicating a broader host range than previously known [48•]. Because of its wide geographic distribution, it is not surprising that Lassa virus shows considerable genetic diversity. Phylogenetic analyses in the last 20 years reveal that Lassa virus strains form one clade subdivided into 5 or possibly 6 geographic lineages [49–51]. While cross-clade protection has been demonstrated with a vaccine candidate incorporating only the glycoprotein complex of Lineage IV [52], more work will be required to understand the implication of genetic diversity to vaccine and therapeutic monoclonal antibody development.

Did Lassa virus emerge in 1969 as a new virus, a more pathogenic variant of an old virus, or was it simply not recognized. Two missionary workers who had an illness compatible with Lassa fever in 1952 while working in Nigeria were retrospectively diagnosed serologically [30,53], and in 1955, JR Rose described an outbreak of a new disease affecting 7 nurses and 24 other patients with 12 deaths, (39%) at Nixon Memorial Hospital, Segbwema, Sierra Leone. [54] Beyond these events which preceded the original cases in 1969 by only 14–17 years, the trail from published reports is cold. Molecular clock estimates indicate that Lassa virus may have evolved from an ancestral stock 500–1000 years ago [55]. The phylogenetic evidence, wide geographic distribution of Lassa viruses, and especially the association of multiple genotypic lineages with human disease, indicate that it is an old disease that had been medically overlooked or mis-identified.

Conflict of interest statement

Dr Monath is Principal Investigator on a grant proposal submitted to the Coalition for Epidemic Preparedness Innovations (CEPI), concerning advanced development of a Lassa fever vaccine, which is pending award. If awarded he and his company would receive financial support.

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