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AN OUTBREAK OF MAYARO VIRUS DISEASE IN BELTERRA, BRAZIL

I. Clinical and Virological Findings*

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Abstract. An outbreak of human illness caused by Mayaro (MAY) virus occurred in Belterra, Pará, Brazil in the first half of 1978. A total of 55 cases were confirmed, 43 by virus isolation and serology, and 12 by serology alone. The disease in Belterra presented as a distinct clinical syndrome characterized by fever, arthralgia and exanthema. No fatalities could be attributed to MAY virus infection. Arthralgia, accompanied by joint edema in 20% of cases, was a very prominent sign which caused temporary incapacity in many patients. Arthralgia was present in virtually all confirmed cases and persisted in some for at least 2 months, although with decreasing severity. Rash was present in two-thirds of the cases, and was either maculopapular or micropapular. The incidence of rash was higher in children than in adults. Contrary to arthralgia, which started with the onset of clinical illness, rash usually appeared on the 5th day and faded within 3–4 days. Fever, chills, headache, myalgia, lymphadenopathy and other minor clinical manifestations were also recorded, and generally persisted for from 2–5 days. Leucopenia was a constant finding in all cases. Mild albuminuria was seen in four of 25 patients, and slight thrombocytopenia was seen in 10 of 20 cases. The fact that viremia levels higher than 5.0 $\log_{10}$/1.0 ml of blood were recorded in 10 patients raises the possibility that man may be an amplifying host in the MAY virus cycle. The MAY virus illness, as seen in Belterra, has clinical features similar to those observed in persons infected with chikungunya virus.

Mayaro (MAY) virus was originally isolated from five humans resident in southeastern Trinidad in 1954 and takes its name from Mayaro County, Trinidad, the county in which these people resided. Anderson et al.[1] described the clinical illness associated with these original five cases, which consisted of fever of several days duration and generalized systemic complaints of headache, chills and body pain. One patient complained of joint pains and swelling, but rash was not reported, and all patients recovered without complications or relapses.

An outbreak of MAY virus, which occurred at a rock quarry on the Guamá River in Pará, Brazil in 1955, was described by Causey and Maroja.[2] Six strains of MAY virus were recovered during investigations of this outbreak, and these strains, along with those isolated by Anderson et al.[1] in Trinidad, were used by Casals and Whitman[3] in their initial characterization of MAY virus. Clinical illness associated with the Guamá River outbreak resembled that seen in Trinidad. Similar clinical manifestations were exhibited in a case of laboratory infection documented in Belém in 1961 (Belém Virus Laboratory Annual Report, 1961, pp. 39–41), but additionally a transient non-pruritic macular rash on the forearms was noted 2 days before onset of symptoms. The rash reappeared on the 3rd day of illness when the patient was afebrile but still viremic.

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A third outbreak was described by Schaeffer et al.[4] in a report on epidemic jungle fevers during 1955 in a newly formed colony of Okinawan settlers in eastern Bolivia. While several different etiologic agents were probably responsible for this outbreak, only MAY virus was actually isolated. The clinical summary of the single patient from whom MAY virus was isolated is not significantly different from that originally described by Anderson et al.,[1] with the exception that this patient had a mild, generalized maculopapular erythema which appeared on the 6th day of illness and persisted for 2 days. A serological survey of those settlers indicated that 10–15% of the epidemic jungle fever observed in the settlement could be attributed to MAY virus infections.

In February and March of 1978 several cases of an acute febrile disease were observed in Belterra, Pará, Brazil, and three fatalities were recorded. Investigations were begun in March and two arboviruses were identified as responsible for this outbreak: yellow fever (YF) and MAY. All deaths were attributed to YF virus infection. A discussion of the clinical investigations of MAY virus is reported here. Subsequent reports describe the vectors and vertebrate hosts of MAY virus identified during this outbreak, and the epidemiologic investigations.[5,6] A separate report will address our YF virus studies.

MATERIALS AND METHODS

Belterra is a rubber plantation located at the confluence of the Tapajos and Amazon rivers in the northern Brazilian State of Pará. Approximately 4,000 persons resided in Belterra at the time of this outbreak. Detailed descriptions of Belterra, its environs and demographic characteristics are presented in the following reports.[5,6]

Suspect cases of MAY virus infection were actively sought throughout Belterra during investigation of the epidemic. Suspect cases were defined as any person suffering from fever, headache and myalgia, with or without arthralgia or rash. Febrile patients were bled and a clinical history was taken. Blood samples were frozen in liquid nitrogen and transported to Belém where attempts were made to isolate virus by inoculation into suckling mice. In four cases in which the clinical history clearly indicated MAY virus infection but virus was not recovered in suckling mice, attempts were made to isolate virus by directly plaquing whole blood on confluent monolayers of Vero cells grown in 25-cm^2 plastic flasks. Virus isolations were identified by hemagglutination inhibition (HI) or plaque reduction neutralization (PRN) tests using a local reference strain of MAY virus, BeAr 20290.

Selected patients from whom MAY virus was isolated were followed throughout the course of their illness and recovery. These individuals were bled periodically to determine the duration of viremia and onset of detectable antibody. Detailed case histories were also taken from these patients to determine the duration of clinical signs and symptoms of MAY virus infection.

A strain of MAY virus isolated during the Belterra outbreak was compared with two previously isolated MAY virus strains by complement-fixation (CF), HI and PRN tests following standard procedures.[7–10] The MAY virus strains included in these tests were BeH 407, isolated from a febrile patient from the Guamá River outbreak in 1955, and BeAr 20290, isolated from a pool of *Haemagogus* sp. mosquitoes collected along the Belém-Brazilia highway in 1960.

In an effort to rule out other etiologic agents which could potentially cause a clinical syndrome similar to that seen with MAY virus, attempts were made to isolate virus from throat washings, spinal fluids and stool samples collected from suspect cases. Isolation attempts were made in HEP_2 and Vero cells, as well as in suckling mice. In addition, selected sera were assayed by HI for antibody rises or sero-conversions to rubella virus.

RESULTS

Virus isolation and serology

The presence of arthralgia and rash in patients initially raised the possibility of an outbreak of rubella. Hemagglutination-inhibiting antibody to rubella was, however, either absent or present without rise in titer in 14 paired sera obtained from laboratory confirmed cases of MAY virus infection. Since no agent was isolated from stool specimens collected from these patients during the acute phase of illness, enterovirus infection was also excluded as a cause of the rash.

Mayaro virus infection was confirmed in 55 (76%) of 72 persons examined in Belterra during the acute and subacute stages of their illness. Virus isolations were obtained in 43 of these patients, all of whom developed an antibody rise to MAY virus. Primary isolation in suckling mice

TABLE 1

Cross hemagglutination-inhibition (HI), complement-fixation (CF), and plaque reduction neutralization (PRN) tests between prototype strains of Mayaro virus and a representative strain from Belterra

Test	Antigens	Mouse ascitic fluid or serum		
		BeH 407	BeAr 20290	BeH 342376
HI	BeH 407*	160†	320	160
	BeAr 20290‡	160	320	160
	BeH 342376§	160	320	160
CF	BeH 407	32	128	>256
	BeAr 20290	32	128	>256
	BeH 342376	32	128	>256
PRN	BeH 407	473	17,800	35,034
	BeAr 20290	1,272	10,240	40,960
	BeH 342376	640	9,586	37,626

* Prototype Mayaro virus isolated from a person in 1955.
† Reciprocal of serum dilution.
‡ Prototype Mayaro virus isolated from *Haemagogus* mosquitoes in 1960.
§ Human isolate from Belterra.

TABLE 2

Clinical manifestations in 43 patients from whom Mayaro virus was isolated; Belterra, Pará, Brazil, 1978

Symptom or sign	%
Fever	100
Arthralgia	100
Headache	86
Chills	81
Myalgia	74
Rash	67
Lymphadenopathy	53
Dizziness	42
Eye pain	38
Nausea	35
Joint edema	23
Vomit	21
Photophobia	7
Diarrhea	5
Conjunctival congestion	2

yielded 39 isolates and an additional four sera yielded virus when tested in Vero cell culture, although initially negative in mice. Reisolation of virus from all 43 specimens was achieved by direct plaquing on Vero cells. An additional 12 cases were identified by serological conversion using HI tests and reference MAY virus antigen.

A comparison was made between a strain of MAY virus isolated during the outbreak in Belterra and two strains previously isolated from the Amazon region of Brazil. Results of this comparison are shown in Table 1. No significant antigenic differences were noted between the Belterra and earlier strains, although some differences in PRN titers were observed.

Mayaro virus was recovered from 30 of 95 blood specimens collected from the 55 laboratory-confirmed cases which represent 27 patients bled more than once, and 28 patients from whom single blood samples were drawn. Virus was isolated from 97% (31 pos./32 tested) of patients bled during the first 24 hours following the onset of symptoms. Recovery rates decreased to 82% (14/17) on day 2, 22% (4/18) on day 3, 7% (1/15) on day 4 and 0% (0/13) on day 5. The single patient whose blood was negative on day 1 was actually bled about 12 hours after the onset of symptoms, and this blood was tested in both mice and Vero cells. This patient was not bled again during the 1st week of illness and was diagnosed only on the basis of subsequent seroconversion. Likewise, the three patients seen on day 2 of illness from whom virus could not be recovered were diagnosed only by seroconversion. The maximum virus titer observed was nearly 4.0 $\log_{10}$ PFU/0.1 ml of whole blood, which was detected on the 1st day of clinical disease.

Mayaro virus could not be recovered from throat washings of 21 viremic patients, nor from the spinal fluid of one viremic patient. In addition, no virus could be isolated from the stools of 14 MAY virus cases collected during the 1st week of their illness.

The fact that infant mouse intracerebral inoculation failed to detect MAY virus in four blood samples which were subsequently shown to be positive in Vero cells raised the possibility that this technique, which has been used for all primary attempts to isolate MAY virus, may not be the best system for its detection. In order to investigate this possibility, 18 blood samples known to contain MAY virus by mouse inoculation were titrated in mice and in Vero cell cultures both under fluid medium and under agar. Mayaro virus was recovered from all 18 samples inoculated in Vero cells, but in only 12 samples in mice. The mean virus titer was 0.4 $\log_{10}$ higher in cells maintained under fluid medium than in those maintained under agar, and the 12 samples positive in mice gave lower average titers than those tested in cell culture.

Clinical findings

The incubation period of MAY virus could not be accurately determined; however, it was ob-

served that one patient developed clinical signs of illness 6 days after entering the epidemic area.

Fever, arthralgia and rash were the most frequently encountered clinical manifestations of MAY virus infection. As seen in Table 2, fever and arthralgia were observed in all 43 patients from whom MAY virus was isolated. Rash was also seen in about two-thirds of these cases. Over 80% of the patients reported headache, myalgia, and chills. Dizziness, eye pain, nausea, vomiting, photophobia, and diarrhea were referred to less frequently. The age of these 43 patients varied from 2–62 years, and both sexes were represented.

Clinical illness usually began with abrupt onset of fever, dizziness, chills, and headache. Axillary temperature was over 39°C in most cases, and reached 40.2°C in one. Arthralgia was a very prominent part of the clinical picture, and many patients referred to it as being quite severe. Wrists, fingers, ankles and toes were predominantly affected, although aches in the elbows and knees were also often reported. Swelling of the affected joints was observed in about 20% of the cases. Several patients reported that arthralgia appeared a few hours before the onset of fever. In some patients the arthralgia was so severe that they were temporarily incapacitated.

Rash associated with MAY virus infection consisted of either small maculopapular or micropapular isolated lesions which occasionally formed small areas of confluence. Rash was generalized in a number of patients and was more prominent on the chest, back, arms and legs, with the face less affected. Lesions were occasionally observed on the hands. In some patients the exanthema was confined to the thorax or the upper limbs. Rash was more commonly observed among children than in older people. Among 80 children less than 5 years old whose parents described a Mayaro-like illness, 71 (89%) reported rash, whereas only 45 (53%) of 85 persons over 50 years questioned reported rash associated with a Mayaro-like illness. Figure 1 presents photographs of a patient with a typical generalized rash who was diagnosed serologically as having MAY virus infection.

Headache was localized in the frontal or occipital regions, and was very severe in some cases. Nausea, vomiting and diarrhea, when present, were usually not severe. Half of the patients presented with inguinal lymphadenopathy, often unilateral and sometimes visible on inspection. These were usually not painful at palpation. No infected cuts or wounds of the lower limbs were noted which could explain this observation. Mild photophobia was referred to by just two of 43 patients. Jaundice, hepatomegaly or splenomegaly was not observed among the patients examined. No congestion of the oropharynx was noted, nor was nuchal rigidity detected. Blood pressure measurements were within normal ranges.

Clinical course

Figure 2 presents a generalized schematic summary of the duration of clinical manifestations of infection with MAY virus, as well as the magnitude and duration of viremia and the onset of detectable HI antibody, as seen in 21 patients with daily clinical follow up for 10 days, and from whom MAY virus was isolated. These patients were also bled periodically after the initial 10-day follow-up, and clinical examinations were performed at subsequent 1–2 week intervals. Values for temperature, viremia and antibody titers are presented as mean values with ranges superimposed. Viremia data is presented on a $\log_{10}$ scale, while antibody is presented as a $\log_2$. Temperatures were measured externally in the axilla. With the exception of the arthralgia, which persisted in some patients for the duration of the 2-month follow-up, clinical manifestations usually lasted from 2–5 days. Rash usually appeared on the 5th day and lasted about 3 days. Hemagglutination-inhibiting antibody was detected as early as day 5 post-onset, and reached maximum titers by day 30.

Although all patients seen remained at home during the acute stage of illness, variation was observed in the severity and duration of symptoms. Thus, whereas some patients became prostrate, in others the clinical manifestations were relatively mild, so that they could resume their activities 2–3 days after the acute phase. No relapses were observed, and no deaths could be attributed to infection with MAY virus. However, 13 days after MAY virus was isolated from one patient, he became ill with YF virus and died 5 days later. Yellow fever virus was recovered from blood and liver samples taken from this patient.

Laboratory findings

Leucopenia was seen within the 1st week of onset in all infected persons, with counts as low as 2,500 white cells per mm^3. Counts performed after the 8th day of illness were within normal limits. With the exception of moderate lympho-

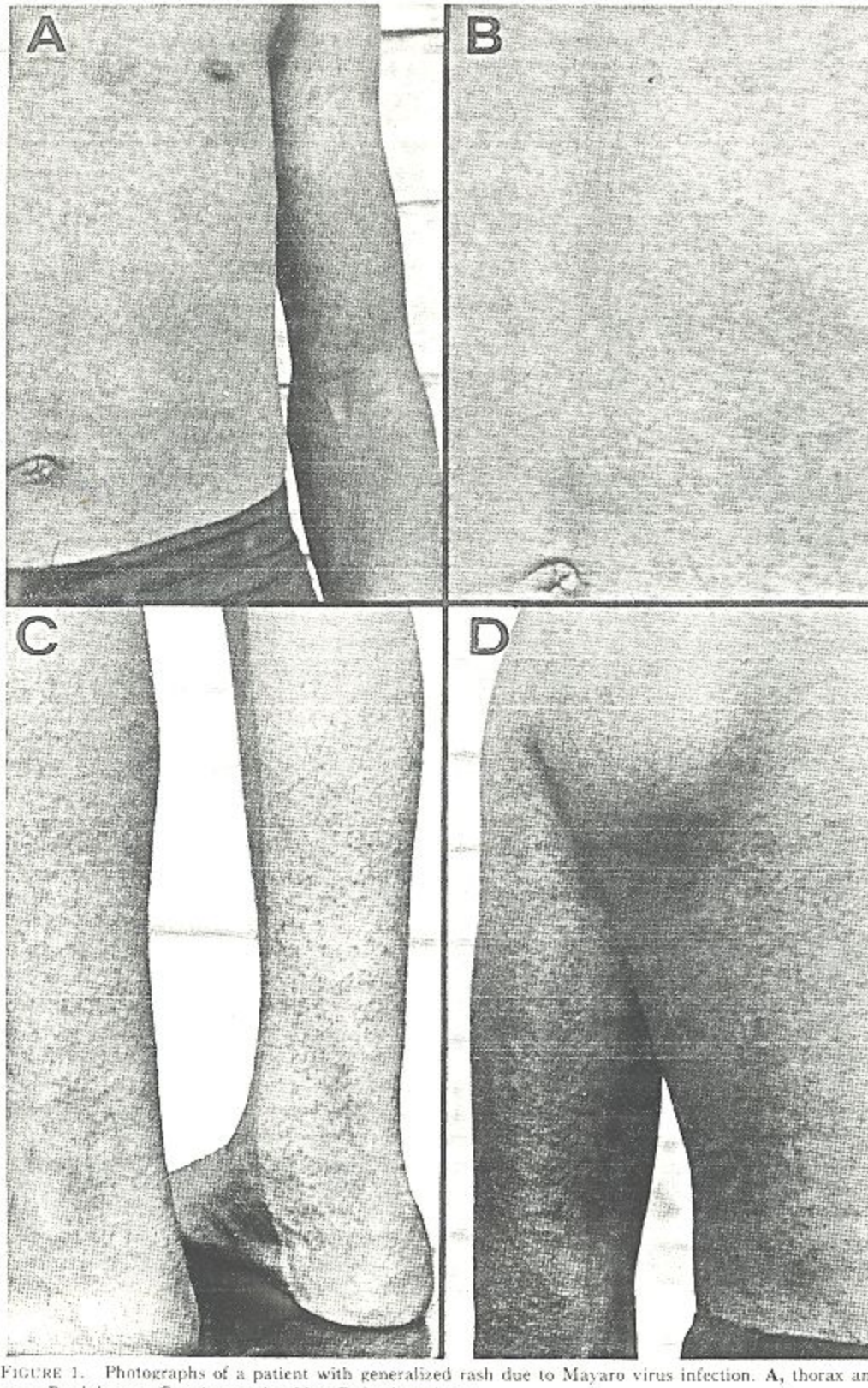

FIGURE 1. Photographs of a patient with generalized rash due to Mayaro virus infection. **A**, thorax and abdomen. **B**, abdomen; **C**, calves and ankles; **D**, back and arm.

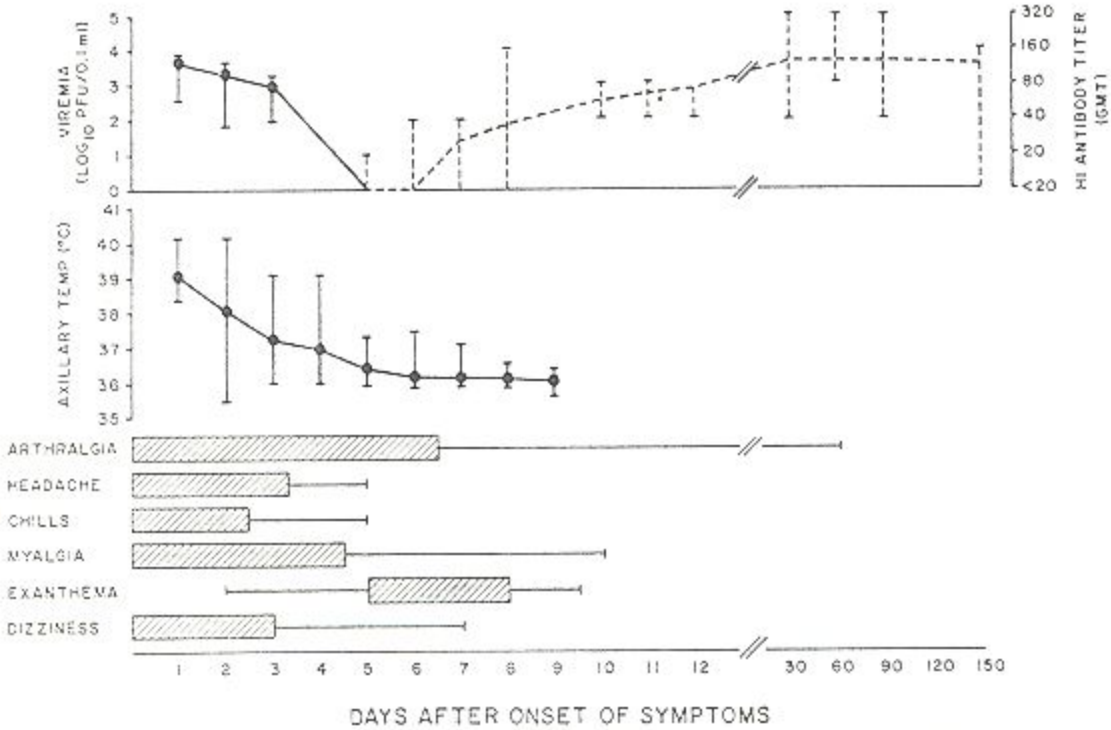

FIGURE 2. Diagrammatic summary of the occurrence of signs and symptoms of Mayaro (MAY) virus infection as seen in 21 patients with daily clinical follow-up through day 10 and periodic follow-up thereafter, and from whom MAY virus was isolated: Belterra, Pará, Brazil, 1978.

cytosis, no changes were observed in differential counts. Urine collected from 25 viremic patients showed the presence of moderate amounts of albumin (2+) in four specimens. In one of these albuminuria could no longer be detected 1 week later. No red blood cells, casts, or other pathological alterations were detected in any urine samples tested. Malaria parasites were not seen in blood smears obtained from 34 viremic patients. Platelet counts were within normal values in 10 patients, but were slightly decreased in 10 others. Serum bilirubin and glutamic-pyruvic transaminase levels were within normal limits in six patients tested. Serum glutamic-oxaloacetic transaminase showed a slight elevation in some patients, usually less than 100 units per 100 ml of serum.

DISCUSSION

In this outbreak, the clinical signs of fever, arthralgia and exanthema were diagnostic for MAY virus infection. Both fever and arthralgia were seen in all patients from whom virus was isolated, and exanthema was seen in two-thirds. This is in contrast to the other reports of MAY virus infection in which no distinctive clinical syndrome was detected. This distinct syntomatology was later invaluable in our epidemiological studies, because patients readily recalled the disease and could frequently recall the exact dates when they were ill.

Arthralgia was recorded in only one of five cases in Trinidad, and not noted in the six patients seen in the Guamá River outbreak or in the single patient from whom MAY virus was isolated in the Bolivian study.[1-2,4] Likewise, exanthema was only reported for the Bolivian patient[1] and the patient with a laboratory infection in Belém, Brazil. The fact that all confirmed patients seen in the Belterra outbreak complained of arthralgia, and two-thirds presented with an exanthema, suggests that the strain of MAY virus which caused this outbreak may have been more virulent or this population more susceptible. Serological comparison of a MAY virus strain isolated during the Belterra outbreak with two previously isolated strains from Brazil failed, however, to detect significant antigenic differences.

Inguinal lymphadenopathy, which was noted

in half the cases, has previously not been reported for MAY virus infection. The remainder of the clinical manifestations including fever, headache, chills, myalgias, dizziness and nausea observed in Belterra have been recorded in the past. Light icterus, which was reported by Causey and Maroja,[2] was not seen in Belterra. In fact, bilirubin serum levels of six Belterra patients were within normal limits. Polyuria was reported in the Bolivian case,[4] but was not observed during the Belterra epidemic. The finding of mild albuminuria in four Belterra cases is difficult to interpret, although one can assume that this was a temporary alteration, since it could not be detected in the urine of a patient sampled 1 week later.

Results presented here indicate that the duration of viremia in patients is at most 4 days, and significant titer, were observed on at least 3 of these 4 days. This raises the possibility that man may serve as an amplifying host in the transmission of MAY virus during epidemics. While the quantity of virus needed to infect feeding vectors has not been determined, it appears that man may circulate virus in sufficient quantities to infect some feeding vectors. However, most patients observed during the acute stage of illness were not continuing their daily activities, and many were bedridden. Consequently, unless viremia occurs prior to the onset of symptoms, only vectors found in or near residences would be expected to be exposed to viremic patients.

The close antigenic similarities between MAY and chikungunya (CHIK) viruses have been well documented;[11] however, a comparison of the clinical illness resulting from infection with the respective viruses has yet to be made. The epidemic investigated in Belterra provided the first opportunity to observe a significant number of MAY virus infections, thus allowing an estimation of the relative frequency and duration of clinical signs and symptoms. These observations provide a data base which now allows us to compare the clinical symptomatology of MAY and CHIK virus-induced diseases.

The clinical similarities between these two viruses are found to be quite striking on comparison. Infection with CHIK virus, as described following the first recognized epidemic in Tanzania,[12] and later reiterated by studies in India,[13-15] Thailand,[16] and Vietnam,[17] is characterized by sudden onset of high fever and joint pains, and followed somewhat later by rash in the majority of patients. This syndrome is just as has been described here for infection with MAY virus. Likewise, headache, myalgia and lymphadenopathy are frequently encountered among patients suffering from infection with either virus. The febrile response, viremia intensity and duration, and the immune response following infection by each virus also appears to be almost identical. Persistent arthralgia, occasionally for considerable lengths of time, appears to be a common characteristic as well. Lumsden reported that the clinical uniqueness of the disease caused by CHIK virus among Tanzanians was readily recognized by the people and "there was never any doubt in their minds as to whether or not they had or had not experienced an attack."[18] This, too, was our experience while investigating the MAY virus epidemic in Belterra. Hemorrhagic manifestations, and rarely death, have been attributed to CHIK virus infection in Asia.[13-15] While we observed neither at Belterra, it is possible that these characteristics may pertain to MAY virus infections as well, but are only seen infrequently.

Experimental infections of rhesus monkeys (*Macaca mulatta*) with both CHIK and MAY viruses have been attempted previously.[19] Monkeys infected with either virus showed similar clinical responses. More importantly, when these monkeys were subsequently challenged with the heterologous virus, none had a detectable viremia, indicating cross-protection. Should this observation hold true with regard to humans, it may explain in part the mutually exclusive distribution patterns of these viruses. Cross-protection between these viruses also holds relevance in terms of vaccine production and efficacy.

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