A new public health problem in India is described in the following account. This is Kyasanur Forest Disease, a tick-borne virus disease, which affects man and certain wild monkeys and was first recognized in 1957.

VIROLOGICAL EPIDEMIOLOGY OF THE 1958 EPIDEMIC OF KYASANUR FOREST DISEASE

Telford H. Work, M.D., M.P.H., F.A.P.H.A.; F. R. Roderiguez, M.B.B.S.; and P. N. Bhatt, M.P.H.

AN IMPORTANT new public health problem in India was recognized in March, 1957, when Kyasanur Forest Disease (KFD) was first described in Shimoga District of Mysore State.[1-3] The infected area is situated just under 2,000 feet elevation in the eastern foothills of the Western Ghats in Mysore as shown in Figure 1. The area is about ten miles square and receives an annual rainfall varying from 30 to 80 inches east to west, according to locality. The general terrain is hilly, covered by intermittent tropical evergreen and deciduous forest which is contiguous north and south for hundreds of miles along the Western Ghats. The forest is interspersed with open, low-lying areas where rice and other crops are cultivated. Villages are usually situated adjacent to the forest at the edge of cultivated areas.

Large numbers of wild monkeys of two species, black-faced Presbytis entellus and red-faced Macaca radiata, inhabit the forest. It was from blood of a Presbytis entellus found moribund in Kyasanur Forest that the first isolation of KFD virus was obtained. Accounts of investigations which defined the etiology and epidemiology of KFD have already been published.[4]

Although caused by a tick-borne virus of the Russian spring-summer (RSS) virus complex, usually associated with central nervous system disease in man,[5] KFD manifests itself as a hemorrhagic fever in more severe cases.[2] As yet, no direct involvement of the human CNS by the virus has been observed, and the disease appears to be very similar to Omsk hemorrhagic fever of Siberia described by Chumakov.[6,7]

Clinical Features

The disease is characterized by a sudden onset of fever and/or headache five to eight days after forest exposure. This is followed shortly by severe pains in the neck (meningismus), low back, and extremities, accompanied by severe prostration and marked inflammation of the scleral and palpebral conjunctivae. An important diagnostic sign in some patients is a papulo-vesicular eruption on the soft palate. Vomiting and diarrhea frequently occur two or three days after onset. Hemorrhagic signs such as bleeding gums, epistaxis, hemoptysis, hematemesis, melena and frank red blood in the stools appear at this time. The fever lasts from five to 14 days with an occasional febrile exacerbation in the third week. Convalescence is prolonged.

No changes have been detected in cerebrospinal fluid. There is invariably

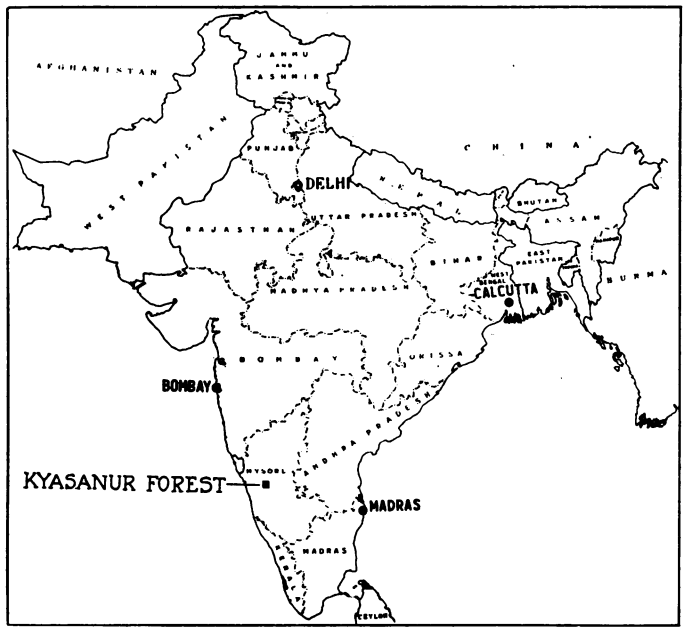

Figure 1

a marked leucopenia with an accompanying thrombocytopenia. Beginning about the fourth day and lasting for the duration of fever, granular casts and red cells may appear in the urine. Death occurs usually in the second week and results from hemorrhagic complications; either oozing of blood into the lungs as a precursor to pneumonia or massive exsanguination into the gastrointestinal tract. Post-mortem histology has shown focal necrosis in the liver and sloughing of tubular epithelium in the kidney.

Diagnosis

KFD virus has been observed to circulate in the blood from two days before until as long as ten days after onset of the disease. The virus is remarkably stable in blood serum and is easily isolated by intracerebral inoculation into infant or adult mice. Isolation of virus from blood collected during the acute phase of illness has been the most frequent laboratory substantiation of a clinical diagnosis. Complement-fixation tests using suspensions of first passage mouse brains as crude antigens against standard immune serums provide an early identification of the agent. This often gives a laboratory diagnosis before a convalescent serum specimen showing an increase in specific antibodies can be collected. Some cases seen for the first time late in the illness were diagnosed exclusively by serology.

Epidemiology in 1957

Investigations which led to description of Kyasanur Forest Disease and established an RSS viral etiology were begun by the Virus Research Centre late in March, 1957, almost three months after the first cases of that year had been reported as enteric fever. Retrospective serological diagnosis of these cases and increasing efficiency in laboratory diagnosis of cases reported in April, May,

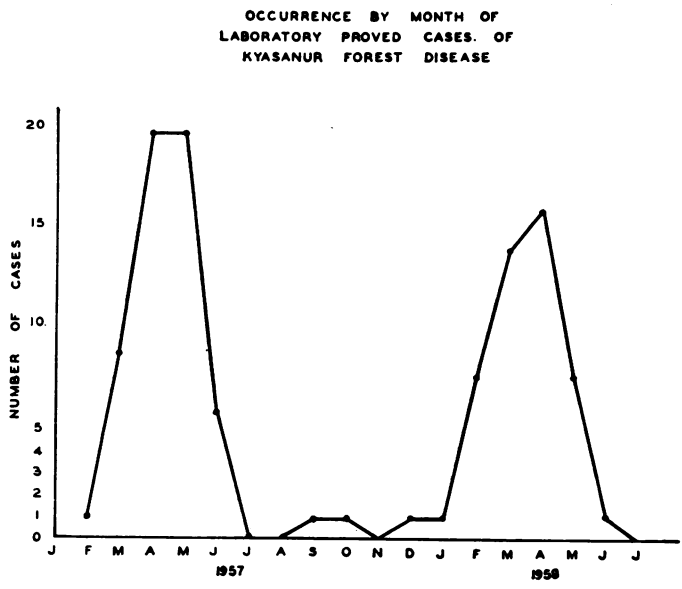

Figure 2

and June provided data indicating a seasonal incidence of human cases as shown in Figure 2. Soon after onset of the monsoon rains early in June, human cases of KFD ceased, probably because of the change of activity of the tick vectors within the forest and the fact that during the heavy rains the villagers spend little time in the forest and engage instead in the cultivation of rice in open fields outside the forest. It is important to note that the period from January to June is the spring and summer season in this part of India, and that in these months the ticks are at maximum activity.

Because the 1957 epidemic obviously terminated with the onset of the annual monsoon rains in June and another began at the end of the monsoon season, the epidemic year was defined as beginning in September and ending in August. Hence, data concerning virus isolations (Table 1) and cases diagnosed (Figure 2) are presented in this manner.

The mortality rate in the 1956-1957 epidemic of almost 500 reported cases was approximately 10 per cent. A number of reported cases were proved in the laboratory not to be KFD, but it is probable that under the circumstances of incomplete epidemiological coverage prevailing at that time at least as many genuine cases were not reported. The

Table 1—Isolations of Kyasanur Forest Disease Virus from Human Patients, Wild Monkeys, and Haemaphysalis Ticks

Period / Source	1957 Epidemic						1957-58 Epidemic											Total
	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	
Human Serum	2	9	14	4	0	0	1	1	0	0	0	5	8	9	7	1	0	0	61
Wild Monkeys	3	0	1	1	0	1	0	0	0	0	1	1	0	2	1	0	0	0	11
Haemaphysalis ticks	2	0	0	0	2	8	4	0	0	0	0	0	0	0	0	0	0	0	16
Total	7	9	15	5	2	8	5	1	0	0	1	6	8	11	8	1	0	0	88

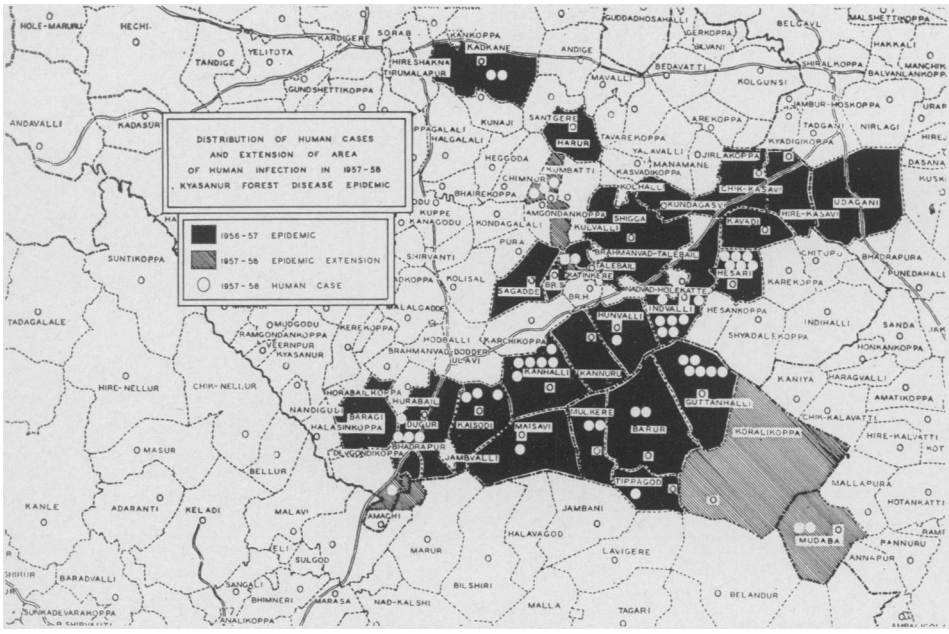

Figure 3

situation was especially serious in that the disease occurred predominantly in young adult males who were actively engaged in forest occupations on which families and villages were dependent. The large number of young adults afflicted with such a prolonged, prostrating disease constituted a serious loss of manpower during the pre-monsoon season when stocks of firewood and building materials were being collected and fields prepared for the one crop of rice cultivated each year during the monsoon season, June to October.

Epidemiological investigations established that the disease had not affected man or monkeys in the presently known infected area prior to December, 1955. During the first epidemic season, January through April, 1956, not more than four villages were affected. In 1957, however, more than 20 villages were affected, a demonstration of the rapid spread of the infection. The black area in Figure 3 encompasses these villages.

Dead monkeys were found in the human epidemic and adjacent areas throughout the year. KFD virus was isolated from dead monkeys autopsied in the forest in March, May, June, and August, 1957.[8] The virus was also isolated repeatedly from Haemaphysalis ticks—at least ten strains from H. spinigera—collected in Kyasanur Forest.[8,9] Ticks of this genus, including large numbers of H. spinigera, were taken from monkeys and birds collected in and around the known infected forest areas. Serological studies showed that a substantial percentage of certain species of rodents contained specific neutralizing antibodies to KFD virus, while serum specimens from the same species collected outside the area were entirely negative.

By the end of 1957, accumulated data provided evidence that: (1) there had been a recent introduction of an RSS tick-borne virus into a forested area of Shimoga District, (2) the virus caused a new and fatal disease of indigenous human beings and monkeys, (3) there

was rapid extension of the infection to new localities where human beings were being infected, (4) Haemaphysalis spinigera ticks, which feed commonly on monkeys and birds as well as man, were infected and appeared to be the vector, and (5) antibodies in rodents indicated a separate, nonprimate cycle by which the infection might be not only maintained but also spread. It was, therefore, imperative to intensify epidemiological studies in man and, secondarily, in monkeys, ticks, and other vertebrates during the 1957-1958 spring and summer season to determine how fast, how far, and in what direction the infection would spread as an index to the size of the public health problem that KFD might become.

1958 Epidemic

In April, 1957, a field laboratory had been established in Sagar by the Virus Research Centre for collecting, processing, and transmitting human, primate, rodent, avian, and arthropod specimens to the main laboratory in Poona. Specimens were collected primarily by medical, entomological, zoological, and subsidiary personnel of the VRC staff in close collaboration with Dr. D. P. Narasimha Murthy, medical officer of health of the Sagar Secondary Health Centre; Dr. Prasenna Iyengar, Ulavi Primary Health Centre medical officer; Dr. R. Laxmana Rao, assistant surgeon of the Combined Hospital in Sagar; and Dr. Riaz Ahmed, medical officer of health, Sorab Secondary Centre, who received reports of suspected cases through hospitals, dispensaries, and a staff of health inspectors. The VRC staff worked in close collaboration with the Mysore government medical and public health officers in collecting specimens and following up reports of dead monkeys. In turn, they reported to the Mysore officials new cases discovered in the course of these field investigations.

In January, 1958, the VRC medical and field staff in Sagar was augmented to intensify investigation of reported KFD cases and wild monkey deaths. Although the outbreak reached epidemic proportions later than anticipated, the activity of these field personnel was efficient enough to establish the diagnosis in 32 of 51 cases studied by virus isolation, as described earlier in this presentation.

Table 1 shows the incidence of virus isolations by month. It is apparent that the disease again affected the forest villagers seriously. The incidence of infections in children, teenagers, and old people was greater than in the 1957 epidemic, owing probably to a greater number of immunes in the most highly exposed middle-age group.

KFD virus was isolated in January, February, April, and May of the 1958 epidemic from wild monkeys found dead in the infected area. The simultaneous epizootic in monkeys indicates that the monkeys are valuable sentinels and could provide a mechanism for spread of the infection to new localities as in sylvan yellow fever. However, antibody studies failed to demonstrate neutralizing antibodies in serums of healthy monkeys collected anywhere outside this epidemic area. A significant incidence of KFD-positive monkeys within the epidemic area showed that many monkeys survive the infection, an observation supported by experimental infection in the laboratory. Study of the entire experience of virus isolation from human, monkey, and tick hosts from March, 1957, through August, 1958, indicates that, within limitations of the collecting technics, virus was recovered in almost every month and must therefore have been permanently established in the area.

Allowing for greater efficiency of collecting and serological follow-up in the more intensive epidemiological coverage in 1958, the actual number of cases was fewer than in 1957, although curves for

laboratory proved cases in the two epidemics in Figure 2 appear to be similar. It should be noted that there is an earlier cessation of cases in 1958; cases are diminishing in April and have ceased by the end of May. This pattern was the result of unseasonal rains early in April, which produced monsoon conditions about six weeks earlier than in 1957 and were thus a major factor in limiting the number of cases in 1958. There were 466 reported cases in 1957 compared to only 181 in 1958 and the mortality rate dropped from 10 to 3 per cent.

Figure 3 provides the most important information resulting from locating the laboratory proved cases of 1958 on a map of the area known to be infected in 1957. Almost all cases occurred in the previously infected area. However, it is important to note that the cases occurring in new, adjacent areas were found early in the season. It is obvious that the rapid spread of 1957 did not continue in 1958, aborted in part, perhaps, by the early rains. The occurrence of significant numbers of cases in 1958 in the 1957 epidemic area is further evidence that the infection is well and probably permanently established in that region and will continue to be a threat to nonimmune, unprotected persons exposed in the infected forest areas.

What factors, beyond change in temperature, humidity, and rainfall, contribute to a rapid extension in one year and limited extension in another are unknown but determination of these factors is the object of long-term field investigations which are continuing.

REFERENCES

1. Work, T. H., and Trapido, H. Summary of Preliminary Report of Investigations of the Virus Research Centre on an Epidemic Disease Affecting Forest Villagers and Wild Monkeys of Shimoga District, Mysore. Indian J. M. Sc. 11:340–341, 1957.
2. Work, T. H.; Trapido, H.; Narasimha Murthy, D. P.; Laxmana Rao, R.; Bhatt, P. N.; and Kulkarni, K. G. Kyasanur Forest Disease III: A Preliminary Report on the Nature of the Infection and Clinical Manifestations in Human Beings. Ibid. 11:619–645, 1957.
3. Narasimha Murthy, D. P. New Virus Disease—Kyasanur Forest Disease. J. Indian M. A. 31:125–126, 1958.
4. Work, T. H. Russian Spring-Summer Virus in India—Kyasanur Forest Disease. Progr. Med. Virol. 1:248–277. Karger, Basel/New York, 1958.
5. Smorodintsev, A. A. Tick-Borne Spring-Summer Encephalitis. Ibid. 1:210–248. Karger, Basel/New York, 1958.
6. Chumakov, M. P. K Itogam Ekspeditsii Instituta Nevrologii Po Izucheniiu Omskoi Gemorragicheskoi Likhoradki (OL) (Results of the Study Made of Omsk Hemorrhagic Fever (OL) by an Expedition of the Institute of Neurology). Vestn. Akad. Med. Nauk. 2:19–28, 1948.
7. ————. Tick-Borne Hemorrhagic Disease in the U.S.S.R. Proc. VIth Int. Cong. Trop. Med. & Mal., Lisbon. (To be published.)
8. Bhatt, P. N.; Work, T. H.; Varma, M. G. R.; Trapido, H.; Narasimha Murthy, D. P.; and Roderiguez, F. R. Kyasanur Forest Disease IV: Isolation of Kyasanur Forest Disease Virus Strains from Infected Human Beings and Monkeys of Shimoga District, Mysore State. (In preparation.)
9. Trapido, H.; Rajagopalan, P. K.; Work, T. H.; and Varma, M. G. R. Kyasanur Forest Disease VIII: Isolation of Kyasanur Forest Disease Virus from Naturally Infected Ticks of the Genus *Haemaphysalis*. Indian J. Med. Res. (In press.)

Dr. Work was director, Indian Council of Medical Research Virus Research Centre, Poona, India, 1955-1958, and now is staff member, Rockefeller Foundation, New York, N. Y. Drs. Roderiguez and Bhatt are assistant research officer and research officer, respectively, Virus Research Centre, Poona, India.

This paper was presented before the Epidemiology Section of the American Public Health Association at the Eighty-Sixth Annual Meeting in St. Louis, Mo., October 30, 1958.