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East Africa High Commission:
(5) Virus Research Institute

Washington, D.C.
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Mr. Walter S. Rogers
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522 Fifth Avenue
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Dear Mr. Rogers:

The Virus Research Institute was formerly the Yellow Fever Research Institute, which was under the direction of the Rockefeller Foundation from 1936-1949. The Yellow Fever Research Institute was founded in 1936 as a result of decisions reached that year in London between representatives of the International Health Division of the Rockefeller Foundation and the Colonial Office, and "the scientific administration was under the control of" the Foundation.[1] The principal project of the Foundation was the study of a possible recurrence or spread of yellow fever, with special reference to India and the Far East. The Institute had excellent laboratory facilities in the former Human Trypanosomiasis Institute (erected in 1931) which were made available by the Government of Uganda. The scientific staff included a Director, two or three research workers appointed by the Rockefeller Foundation, and other workers seconded from the Uganda Medical Department or directly appointed by the Secretary of State for the Colonies.

The main work of the Yellow Fever Research Institute was an intensive investigation of the epidemiology of yellow fever in a rain forest area near Bwamba in west Uganda which led to the isolation of yellow fever virus in Aedes africanus in 1948. The Institute also carried out immunity surveys in East and Central Africa, tested and distributed yellow fever vaccine prepared by the Rockefeller Foundation in New York, and made histological examinations of specimens of liver obtained at post-mortems or by the viscerotome. Several new viruses were isolated during investigations into yellow fever and studies of the properties and relationships of these viruses, although a secondary object, were also carried on. At the end of 1949 the connection with the Rockefeller Foundation was officially terminated. On January 1, 1950, the Institute, renamed the Virus Research Institute to indicate the wider scope of its program, became a unit of the Colonial Medical Research Service administered by the High Commission, and it was officially taken over by the High Commission on April 1, 1950. The Institute was one of the medical research units established at the initiative of the Colonial Medical Research Committee.

The Institute, as a medical research unit, is responsible to the High Commission through the Administrator. Although the High Commission has administrative responsibility for the unit, the Colonial Medical Research Committee retains scientific oversight through an Advisory Council which visits East Africa once each year.

The authorized scientific and technical staff of the Institute has been the same as that of the Yellow Fever Research Institute at the end of 1949, except for a newly created post of Zoologist. Until the end of 1951 the authorized European staff included a Director, one pathologist, an epidemiologist, two entomologists, a medical research officer, and a zoologist, three laboratory technicians and an office staff of four. There had been no difficulty in recruiting scientific or technical staff after the war and the staff was at full strength at the end of 1950. In 1951, however, some vacancies occurred. Two professional posts were vacant; the successor to the pathologist who left in September 1951 was replaced in 1952, but the post of zoologist was held in abeyance due to lack of funds. There was also one vacancy through 1951-52 among the authorized laboratory staff and one clerical vacancy. The laboratory vacancy was filled in late 1953.

Overseas training has been enjoyed by several members of the staff. The pathologist returned in April 1950 from two years' study of virus research in the United States, during which he held a one year Travelling Fellowship from the Rockefeller Foundation. The medical research worker, also on a Rockefeller Travelling Fellowship, spent a year studying virus work in institutes in the United States, including the Army Medical Center, Washington, D.C. and the Rocky Mountain Laboratory, and returned to the Institute in October 1951. The epidemiologist was posted to the Ministry of Health in London for three months early in 1950.

Present accommodation at Entebbe consists of the main laboratories, including a new wing added in 1949-1950, three special houses for mouse breeding, extensive accommodation for monkeys, rabbits, guinea-pigs, poultry and several stores, a well-equipped workshop and a garage for the Institute's three vans, housing accommodation for the Director and scientific staff. During 1952 the laboratories were reorganized to provide space for visiting workers.

The main Institute building with laboratories and three staff houses formerly belonging to the Yellow Fever Research Institute, were handed over as a free gift by the Government of Uganda for so long as they are used for their present purpose. The new wing of the Institute, the Director's house and four staff houses were erected in 1949-1950 from funds supplied under C.D.&W. schemes. The scientific equipment of the former institute, valued at $25,000 and including some of the latest and more expensive apparatus made in the United States, was presented as a gift by the Director of the Rockefeller Foundation.

As planned at the time of the establishment of the Institute, a grant from C.D.&W. Research Allocation was made for five years to cover all capital and 75 percent of the recurrent expenditures, the remainder of which would be contributed by the East and Central African Governments. Expenditures of the Institute in 1950, the only year for which figures are available, totalled £22,204, of which £21,949 was recurrent expenditure and only £255 extraordinary. Revenue was £1,127. Under C.D.&W. Scheme R. 395, all extraordinary expenditure and 75 percent of net recurrent

expenditure (£20,822) was paid by C.D.&W. funds. The remaining 25 percent of recurrent expenses was provided by equal contributions from Kenya, Uganda and Tanganyika, which together supplied over 90 percent of this amount, with much smaller contributions from Zanzibar, Nyasaland and Northern Rhodesia. At present total recurrent expenditures are reported to remain constant at £35,000 each year, with a progressively larger proportion going for salaries each year, and a smaller amount for other research expenditures.

The stated purpose of the Institute continued to be "the search for, and recording of, the basic data on the epidemiological aspects of yellow fever in East Africa."[2] Its scope, however, was enlarged to include investigations into known and suspected virus and rickettsial diseases in the three East African mainland territories, Zanzibar, Northern Rhodesia and Nyasaland. After 1952 the main purpose was restated by the new Director as "the investigation of viruses for the benefit of the supporting territories."[3] Also included in researches were studies of wild animals, especially monkeys, as reservoirs of virus diseases affecting man, and studies of the insect vectors. The Director felt in 1950 that the Institute in its work should concentrate on investigation into practical field problems since it is impossible to carry out in Africa the more fundamental researches on the physico-chemical aspects of viruses which would require large laboratories.

The Institute's program of work was formulated in consultation with the Directors of Medical Services of the six territories. At the end of 1949 each of them was requested to state his problems and if possible to give an approximate order of priority. In the replies there was unanimous agreement that yellow fever was most important, but there seemed to be no other viruses or rickettsial diseases of general importance. During 1950 the Director of the Institute visited all the mainland territories and held discussions with each of the Directors of Medical Services. On this basis a general long-term program was planned in which yellow fever was given first priority and rickettsial infections and encephalitic diseases were given second priority. This program, however, was not exclusive, and, on the request of the Directors of Medical Services, other investigations on virus diseases would be undertaken provided staff was available.

Probably the more publicized activity of the Institute since the beginning of 1951 has been its participation, along with the South African Institute for Medical Research, in the WHO-sponsored project of mapping the southernmost boundary of the yellow fever endemic area in Africa which includes all of East Africa. It was intended that a total of about 10,000 protection tests - "The fundamental weapon of all virus research"[4] - would be made, the expenses being paid by WHO. Of these about 7,500, from the Belgian Congo, Northern Rhodesia, Nyasaland and Tanganyika, Zanzibar and Pemba, and from Angola until the Virus Institute in Lisbon was ready to take over, have been carried out at Entebbe; the remainder, from South West Africa, Bechuanaland, Southern Rhodesia, Mozambique and the Union of South Africa were to be done by the South African Institute When the work was completed, proposals for the delimitation of the boundary would be drawn up at a meeting of the authorities concerned and presented to the Yellow Fever Panel and Expert Committee of WHO. Immune sera were found in all the territories whose specimens were tested at Entebbe. The WHO Expert Committee on Yellow Fever dealt with the delimitation of the endemic zone at its meeting in Kampala in September, 1953.

Most of the Institute's work on the epidemiology of yellow fever centered on the problem in dry areas. The Yellow Fever Research Institute, after many years of work on the epidemiology of yellow fever in the western Uganda rain forest area, proved by 1948 that the principal mammalian hosts of yellow fever in these areas are various species of African monkeys. The monkeys continuously maintained the disease, and showed a high incidence of immunity without any signs of illness in areas where there was little evidence of the disease in man; they were therefore satisfactory indicators of virus activity. The Institute also proved that there were two cycles in the transmission of the disease, an Aëdes Africanus-monkey cycle in the forest canopy and a monkey-A.simpsoni-human cycle. These conclusions, however, had not been found valid for areas with a prolonged dry season where yellow fever is endemic even though the mosquito vectors are reduced to very small numbers or disappear entirely during the dry period. The Virus Research Institute therefore undertook a study on the continued survival of yellow fever virus in areas with pronounced dry seasons.

A suggestion that transovarial transmission of the virus in infected mosquitoes might aid the survival of the virus during the dry season - an idea forwarded by various workers in the past - was not supported by the results of extensive laboratory experiments on A. africanus carried out in 1950. In March of the same year a combined immunity and entomological survey was carried out in one area with a prolonged dry season - the West Nile District of Uganda. Although valuable data on the incidence of immunity in the human and monkey populations, and on mosquitoes was obtained, the problem was not solved.

In 1951 the investigations continued in two other dry areas. Epidemiological surveys were carried out in the Gede and Taveta areas of the Coast Province, Kenya, and later a preliminary survey was made in the Karamoja District of the Northern Province of Uganda in the hope of finding a locality with conditions similar to those on the coast but closer to the Institute for further investigations. Work in these areas suggested that the epidemiology of yellow fever in drier areas with prolonged dry seasons is likely to be entirely different from the Uganda wet forest cycle. Bush babies - both the larger species Galago crassicaudatus and the small G. senegalensis - rather than monkeys may be the principal animal hosts of yellow fever in these areas. In the known infected areas of Kenya (Coast Province and others) the Institute workers found a much higher incidence of immunity among bush babies than among monkeys. In Karamoja in 1951 the Institute found almost 28 percent of bush babies immune while no immune hyraxes or monkeys were found. Large collections of bush babies were made in Karamoja in 1952 and evidence was obtained that yellow fever exists among them. The main practical conclusion is that in Kenya (and probably in the driest parts of Uganda) monkeys do not serve as a reliable indicator of the presence or absence of active yellow fever virus as they do in wet forest areas. Earlier conclusions that certain localities were free of yellow fever, on the basis of monkey tests, were questionable until confirmed by a study of an adequate sample of bush babies. The Institute also proposed that in Kenya studies of monkeys were of no value in determining the range and intensity of virus activity, while studies of bush babies were.

The Institute also concluded that A. africanus mosquito probably does not play an important part in the dry country cycle. In dry areas mosquitoes disappear or are reduced to very small numbers for long periods and the chain of transmission is broken. Moreover, it is improbable that the mosquito could transmit the disease from one bush baby to another since the latter are active at night and protected while sleeping during the day. In search of the insect which carries the virus from one bush baby to another, extensive surveys of biting insects were made during 1951 in the Coast Province and Karamoja. Mites were found in the nests in the treeholes in which galagos sleep and on their bodies. Mite cultures were started at Entebbe and transmission experiments with mites and yellow fever virus were planned.

A study of the biting habits of Aedes simpsoni, the mosquito which transmits yellow fever from monkey to man and from man to man in the wet forest areas of Uganda, was undertaken. This study was intended to ascertain whether non-biting habits of the mosquito explained the fact that the human immunity rate throughout most of Uganda was negliginle even though the conditions required by this mosquito are found in many parts of the country. It was found that A. simpsoni occurred as anthropophilic and presumably zoophilic populations, and the presence of the latter explained the absence of yellow fever in some areas. No conclusions were drawn as to whether the two groups were distinct physiologically or whether differences in environment, including alternative hosts, determine the differences in biting habits. The zoophilic appeared to be limited to higher altitudes and temperature might be a relevant environmental factor, but no generalizations could be made by the end of 1951. The practical implication was that a preliminary study should be made on biting behavior of the species in a given area before public funds are spent on attempts to control mosquitoes in rural areas by repeated inspection of plantations and removal of important food plants.

Research to determine the value of inoculating standard yellow fever vaccine and combined yellow fever and smallpox vaccine by the scarification method was successfully completed by the end of 1951. Vaccination against yellow fever by scarification with neurotropic strain had been used in French Africa, with excellent results but with some reactions. The Institute's experiments in 1950 showed that vaccination by scarification with the standard yellow fever vaccine - 17 D strain prepared from chick embryos - which produces no reactions gave a percentage of immunity which was very satisfactory although lower than that obtained with the neurotropic strain. These results were confirmed by a further experiment of the same kind in 1951, which showed a higher percentage of immunity. The next experiment, carried out in 1951, tested vaccination by scarification with the 17 D yellow fever vaccine combined with a smallpox (calf lymph) vaccine. The results with the smallpox vaccine, when in combination with the yellow fever vaccine, were excellent, but the results with the yellow fever vaccine, when mixed with the smallpox vaccine, were less successful than when the vaccine was used unmixed. Simultaneous vaccinations by the unmixed vaccines, however, gave excellent results. Although the mixed vaccine could not be recommended, it was possible to vaccinate at the same time by separate scarifications against both diseases. The new method should effect considerable economies in mass vaccination campaigns in Africa, for the syringes hitherto used for inoculations are expensive and easily broken in sterilization when large numbers are handled. However, before the double vaccination can be recommended as a universal routine further studies will be necessary on the reactions of whites.

In order to determine the period of immunity to yellow fever after vaccination with 17 D vaccine, the Institute, in November 1950, carried out a survey of vaccinated and unvaccinated populations in Toro District, Uganda, where there had been a mass yellow fever vaccination campaign in 1951. On the basis of the results, the Institute recommended that yellow fever certificates might be extended up to at least nine years after vaccination, except in the case of children who were under seven when vaccinated.

Through 1950 and 1951, in accordance with a request of the Directors of Medical Services of the three territories, samples of all batches of yellow fever vaccine were examined for potency at the Institute and each batch had to be passed as satisfactory before it could be issued for vaccination.

Research has been carried out on a number of hitherto unknown viruses which have been isolated over the years at the Institute during yellow fever investigations. These viruses, like polio, affect the central nervous system in animals and can infect man. Some apparent cases of polio may in fact be caused by one of these viruses and the latter therefore require investigation. Preliminary studies on Uganda S, which was isolated in 1947, were carried on in 1950 and 1951. The virus is capable of infecting men - the sera of four Africans at Bwamba and three from West Nile District were immune- although no human patients have been reported. Another of these viruses, Zika, which was isolated from a monkey in 1947 and from a batch of mosquitoes in 1948, is also capable of infecting man although the symptoms which it can produce are unknown.

Other experiments have been concerned with Mengo Encephalomyelitis Virus, which was first isolated in Mengo District, Uganda, in 1946, and now is known to be one of a widely distributed group of viruses. Confirming results of American investigations, the Institute accumulated evidence during experiments in 1950-1952 that two domestic or semi-domestic species of rats include immunes and play an important role in spreading the infection. The rats excrete the virus in faeces. It is therefore possible that the rat is the natural host of one of the viruses or an unidentified virus and that infection of man and other animals results from accidental contamination of water or food with the excreta of rats. This virus has also been isolated from batches of swamp breeding mosquitoes, but up until the end of 1951 the evidence suggested that the mosquitoes, having picked up the virus from monkeys infected by eating rat excreta, were only carrying the virus mechanically. Transmission experiments in which infected mosquitoes were allowed to bit monkeys failed.

Some survey work was carried out in 1952 on Rift Valley Fever virus which is known to exist in Uganda since it was isolated from mosquitoes in 1944 and human immunes have been reported. No positives were found among human, wild animal and cattle sera from Karamoja.

Studies have been undertaken of fundamental problems concerned with the basic mechanism of virus multiplication to determine the manner in which virus is liberated in the infected cell.

Laboratory studies of Rickettsioses (Typhus Infections) - attempted isolations of rickettsial strains from clinical cases - have been limited because there have been few clinical cases of murine (rat) typhus and even a smaller number of tick typhus cases. Three attempts to isolate in guinea pigs the organisms from three suspected cases of tick typhus failed. In order to determine the frequency of human rickettsial infection in Mengo District, 560 sera from this area were tested with antigens for tick typhus, epidemic and murine typhus, and Q fever. There were 13 positive reactions to the tick typhus antigen while reactions to other antigens were negative. These results were surprising, since clinical cases of tick typhus among the local African population are rare while cases of murine typhus are not uncommon, and were regarded as sub judice until better antigens could be obtained. Attempts to isolate the organism from local ticks (primarily of different species of Rhipicephalus) by inoculation into guinea pigs have failed, none of the guinea pigs becoming immune.

At the request of the Director of the Poliomyelitis Research Center at Johns Hopkins University in Baltimore, U.S.A., the Institute in 1950 collected bloods from a number of isolated localities in Uganda and sent them to him for testing and use in a study of the distribution of types of polio virus in communities with little or no white contact. For the first time, antibodies against the three main types of poliomyelitis virus were found in the bloods taken from isolated areas where no recent cases of the disease had been reported. The discovery suggested that poliomyelitis infection is extremely common among Africans, thus confirming South African findings that a considerable proportion of infants become infected with the virus the first year without showing symptoms of the disease. The Institute also diagnosed cases suspected of being poliomyelitis. In 1951 one death in Northern Frontier District, Kenya, was diagnosed, at the request of the Director, Medical Research Laboratories, Nairobi, has having been caused by polio, and the deaths of two children were diagnosed as not being caused by polio. In 1952 during an outbreak of poliomyelitis in Uganda successful attempts were made to isolate the virus, nine isolations being made.

The Institute has carried out a number of miscellaneous investigations at the request of territorial governments or other organizations. In 1950 specimens from patients suspected of having viral infections, most of them at Mulago Hospital, were examined but no virus was isolated. Thirteen sera received from Uganda and Kenya were also examined for antibodies to various viruses, but no definite diagnosis was made from any of this material. In December 1951 Institute workers cooperated with the Uganda Medical Department in an attempt to ascertain the cause of several apparent cases of mild encephalitis in a number of towns in the Protectorate. At the request of the Northern Rhodesia Government an epidemic of an unknown fever (called Lusaka Fever) in Lusaka in April 1951 was proved, through tests at the Institute, not to be dengue, although the cause remained unknown. At the request of the Director of Stack Medical Laboratories in Khartoum, the Institute determined, by examining bloods for antibodies to yellow fever, that the epidemic of August and September 1951 in Malakal, Anglo-Egyptian Sudan, was not yellow fever. The fulfilling of another request was "a good illustration of how the results of a piece of research, of hitherto purely scientific interest, may suddenly become of considerable practical importance."[5] At the request of the Director of Veterinary Services, Onderstpoort, South Africa, during a severe outbreak of Rift Valley Fever, a dangerous disease of sheep, in southern Free State, a sample of a special strain of virus originally isolated by the Yellow Fever Research Institute in 1944 was sent to him and was later tested as a vaccine in field experiments.

Entomological work included field tick collections to obtain information on seasonal variations in abundance and the diurnal cycle of activity in vegetation, the collection of ectoparasites of trapped mammals, a study of the biting habits of Tabanidae, a great deal of mosquito work, and investigations into the possible eradication of Simulium damnosum from the Victoria Nile.

Zoological studies were made on the respective habits of terrestrial and arboreal monkeys, the latter having the higher yellow fever immunity rate, and a detailed biological study was made of the arboreal redtail monkey. With a view to finding other possible mammal hosts of yellow fever, a program of trapping small terrestrial mammals was carried out in 1950, and the sera was tested, but no yellow fever antibody was found. Field studies on galagos were also carried out in 1952.

The Institute breeds animals essential to virus research. Over 157,000 pure bred white mice, the most important animals in virus research as a whole, were bred at the Institute in 1952. The mouse colony, averaging 25,000, was in 1953 the largest in Africa. Cotton rats have also been bred at the Institute since 1950 and breeding pairs have been sent to the Veterinary Research Laboratories in Kabete, Kenya, and to the Belgian Congo. By the end of 1951 120 Rhesus monkeys had been born in Entebbe, and by March 1953 the total had risen to 130. These animals are essential for the investigation of some diseases such as yellow fever and are normally an expensive item on a research budget since they are usually imported from India. The successful local breeding has saved a considerable sum since 1948, when the last monkey had to be purchased abroad.

Individual members of the Institute's staff "are in close personal touch with" members of the staff of the Rockefeller Laboratories in New York, and collaborative work on some problems has been carried on.[6] Close contact is also maintained with the Rocky Mountain Laboratories, Hamilton, Montana, U.S.A. of the U.S. Public Health Service and with the Virus Laboratories of the South African Institute of Medical Research, Johannesburg. Some of the antigens used by the Institute were provided by these laboratories. Contact is maintained also with the Walter and Eliza Hall Institute in Melbourne. In 1951 visits were paid to the Institute by Dr. J.H.S. Gear of the above mentioned laboratories in Johannesburg and by Dr. L. Van den Berg, the Director of IRSAC, Costermansville, Belgian Congo. The Institute's pathologist attended, by special invitation a symposium on "Immunization against Poliomyelitis" held in Philadelphia during March 1951. In 1952 the head of an American Navy team studying viruses in Egypt visited Entebbe, and the Institute planned to remain in touch with him in the future. Collaboration, possibly on a large scale, with the Institute for Medical Research at Kuala Lumpur on a new program of field virus studies and ecology planned for Malaya and the Far East was contemplated.

Sincerely,

John B. George

P.S.

Footnotes

1. East Africa High Commission, 1951 Digest of the Activities of the Medical Research Organisations, p. 15.

2. East Africa High Commission, Interterritorial Cooperation: Work of the East Africa Central Legislative Assembly, Despatch No. 1/52, 19th May, 1952, from P.E. Mitchell, Chairman, East Africa High Commission, to the Secretary of State for the Colonies, paragraph 57.

3. Interview with Director of Virus Research Institute, September, 1953.

4. East Africa High Commission, 1951 Digest ..., p. 16

5. Ibid., p. 31.

6. East Africa High Commission, Virus Research Institute Annual Report 1950, p. 3.

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