

THE TRANSMISSION OF YELLOW FEVER.*

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(From the Wellcome Bureau of Scientific Research.)

THE mode of transmission in yellow fever is generally considered to have been settled by the work of the famous American Yellow Fever Commission in 1900. (See Senate Documents, 1911.) Practical methods of combating the disease, based on these results, have succeeded to a degree almost unparalleled in the case of any other disease, but although the main conclusions of the Commission, to the effect that yellow fever is transmitted only by the bites of *Stegomyia fasciata* (*Aedes aegypti*), would seem to have been justified in the light of subsequent practical experience, recent investigations have shown that this generalisation requires some modification.

It should be noted that before 1927 all work on yellow fever necessitated the use of human volunteers, and consequently the number of actual transmission experiments is comparatively few. The discovery by Stokes, Bauer and Hudson (1928) that *Macacus rhesus* is susceptible to the infection, has opened the possibility of studying the transmission problem in much greater detail, and as some of these results are at variance with generally accepted views on the subject it seems desirable to re-examine the evidence on which these are based, and also to incorporate recent work, including the results of my own experiments on the subject.

These experiments have been carried out during the past two and a half years at the Wellcome Bureau of Scientific Research, and I should like to take the opportunity of expressing my great indebtedness to Dr. Wenyon and the staff of the Wellcome Foundation for their kind assistance in the course of these investigations. In particular, I should like to mention the very great help I have received from Mr. B. Tazelaar, to whom I am indebted for continual assistance during the whole of this period.

The Virus.

Four strains of yellow fever virus have been studied, three African and one Brazilian, and no marked difference could be found between any of these strains. Vaccination or other methods of immunisation against one strain protected indiscriminately against the other strains, and my results fully support the now generally accepted view as to the identity of the African and American strains of yellow fever. With regard to the behaviour of these strains in monkeys, one of the African strains from Senegal, the first to be established in any laboratories outside endemic regions (Sellards and Hindle, 1928), has shown alterations in its virulence which will be referred to elsewhere. Apart from the results obtained with this modified virus, all the strains have shown a very high degree of virulence in monkeys, the mortality exceeding 95 per cent. in a long series of experiments. In addition to the French strain, experiments have been made with the Asibi strain, from Nigeria, obtained through the kindness of Dr. W. A. Sawyer; a Berlin strain originally from Africa, and a Brazilian strain from Rio de Janeiro, the two last kindly supplied by Prof. M. H. Kuczynski.

COURSE OF INFECTION IN MONKEYS.

The course of yellow fever in *M. rhesus*, whether the disease has been induced by the inoculation of infected material or by the bites of infected mosquitoes, is very constant in its general features, though individual differences may be observed. After an incubation period of two to five days without any prodromal symptoms the temperature suddenly rises 2–3° F. above the normal of the individual, and after 24 to 48 hours the temperature suddenly falls to subnormal, and the monkey generally succumbs within a few hours of this terminal crisis. Occasionally there is a second rise of temperature producing the saddle-back type of temperature chart commonly seen in human cases. It will be noticed that the course of the disease is much more rapid in monkeys than in man, and this difference should be remembered in comparing the two. Human cases of the disease very rarely succumb before the fourth or fifth day of fever, the majority of deaths occurring about the sixth or seventh day, whereas monkeys usually die within two or three days of onset of fever.

Possibly as a result of the longer interval there is a marked difference in the infectivity of the tissues of monkeys and human beings dead of yellow fever. In monkeys the virus often persists in the body until the death of the animal but in man the virus generally disappears before death, or its presence is concealed by the development of immune bodies. A practical result of this difference is that human post-mortem examinations are attended with very little danger of infection, whilst monkeys usually contain the active virus at death, and judging by the number of laboratory infections, in which other sources of infection were excluded, it would seem that especial precautions are necessary in examining these animals.

Kuczynski and Hohenadel (1929) were the first to show that yellow fever virus is present in the blood of monkeys within a few minutes of their inoculation. According to these authors, the virus lives in the blood, at least in the earlier stages of the disease, and consequently may be recovered from the circulation throughout the whole of the incubation period. In one instance they recovered the virus from the blood of a monkey within eight minutes after the inoculation, and in other cases from 4 to 18 hours later. Hudson and Philip (1929) independently confirmed and extended these observations, and showed that the blood of yellow fever monkeys may become infective to mosquitoes within 12 hours after inoculation, and remains infective throughout the incubation period, and at least during the febrile period and for one day afterwards. These authors' experiments, conducted in detail on five rhesus monkeys, are of very great interest, for not only were many batches of mosquitoes fed on the animals on each successive day after being inoculated, but also at the same time samples of blood were taken and inoculated into normal monkeys. Their results clearly indicate that in monkeys the blood usually ceases to be infective to mosquitoes within 24 hours of the first drop in temperature. It should be noted that two of these monkeys showed the saddle-back type of temperature chart often seen in human cases.

The results of these and other experiments, which will be referred to below, indicate that in monkeys the blood commonly ceases to be infective to mosquitoes one to three days after the onset of fever, although the virus may still be present in the blood,

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