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Ecology of the Hosts in Relation to the Transmission of Malaria

BECAUSE the ecology of human malaria has been discussed by many authors, we will focus our main attention on the transmission biology of the malarias of non-human primates; man and his malarias will be included, but only in those situations where the two groups of primates and their parasites become part of the same transmission system.

The level of speciation in the plasmodia of non-human primates is high; 17 species have been described from Asia, 3 from Africa (not including 2 from Madagascan lemurs), and 2 from the New World. The fundamental ecology of the malarias of apes and monkeys is similar to that of the human species. Susceptible mosquitoes must live for a sufficient period of time to allow for completion of sporogony and they must have a predilection for returning to the same group of vertebrates for a second blood meal. In addition, it is essential that the parasite be able to maintain an infection in the vertebrate host long enough for the vector to become infected. Some degree of chronicity is required, too, since either the rapid destruction of the parasite by the vertebrate host or the rapid destruction of the vertebrate host by the parasite would be detrimental, if not fatal, to the maintenance of the transmission system. Our approach to the discussion of the ecology of the malarias of apes and monkeys has for convenience and continuity been organized on a geographical basis.

ASIA

Parts of Southeast Asia are the only areas for which reasonably complete information is available, and proven natural vectors of non-human primate malaria have been identified only from West Malaysia (Wharton and Eyles, 1961; Wharton *et al,* 1962; Eyles *et al,* 1963; and Cheong *et al,* 1965). In 1960, the U.S. Public Health Service (NIH, LPC) established a cooperative project with the Institute for Medical Research in Kuala Lumpur, Malaysia, to investigate the potential for the natural transmission of malaria parasites of monkeys to man. The baseline information on the ecology of malaria in the area was essentially complete because the personnel of the Institute for Medical Research had maintained a high degree of interest in the bionomics of anophelines of the Malay Peninsula for many years.

The NIH-IMR team approached the problem on an ecological basis, studying separately, but by the use of essentially the same techniques, the several distinct types of environments found on the Malay Peninsula which supported monkeys and their malarias (Fig. 1). The basic techniques used in these studies were described in detail by Wharton *et al* (1963). Briefly, they consisted of monkey-baited net traps erected on platforms in the forest canopy and run in conjunction with human-baited net traps, of similar design, on the ground nearby. Mosquito collections were made from these traps from sunset to sunrise, and all

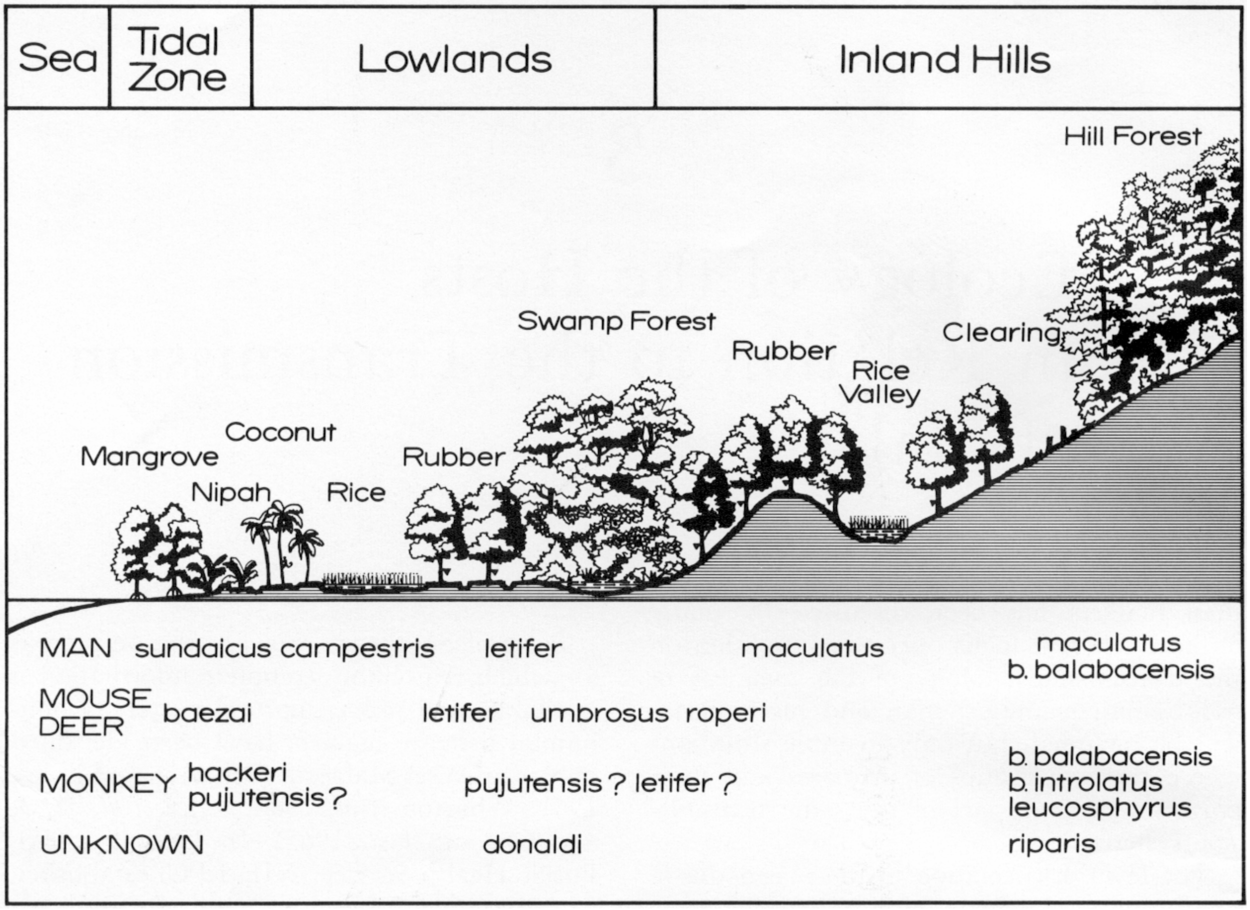

FIGURE 1.—Vectors of human and animal malarias in various ecological zones in West Malaysia (modified from Wharton *et al*, 1964).

anophelines taken in the traps were dissected and examined for malaria parasites. Sporozoite-positive salivary glands were inoculated intravenously into malaria-free rhesus monkeys. The 3 basic types of environments in the area are: fresh water swamp forests, primary rain forests, and mangrove forests.

Fresh Water Swamp Forests. This type of forest covers a large portion of lowland Malaysia either as valleys, in which water collects during the rainy season, or extensive flat areas, which maintain some level of water through much of the year. These areas support considerable populations of monkeys, including both macaques *(Macaca* sp.) and langurs *(Presbytis* sp.). Investigations were conducted in a swamp forest north of Kuala Lumpur, Malaysia where malaria infections had been found in both *Macaca fascicularis* and *M. nemestrina.* The anopheline fauna in this area was dominated by members of the *Anopheles umbrosus* group. Natural malaria infections were known to occur frequently in this species complex in Malaysia and Hodgkin (1956) suspected that some of these infections might be of monkey origin.

As was expected, most of the anophelines caught in human- and monkey-baited net traps belonged to the *A. umbrosus* group, however, *A. letifer* was the only species which invaded the monkey-baited net traps in the canopy in significant numbers. Sporozoites from a large number of naturally infected mosquitoes (including *A. umbrosus* and *A. roperi* as well as *A. letifer)* were inoculated into malaria-free monkeys, but no infections resulted. During the same period, experimental infections were being studied in the laboratory, in Kuala Lumpur, to establish the level of susceptibility of Malaysian anophelines to monkey malaria. *Plasmodium cynomolgi* (B strain), which was originally isolated from *M. irus* (= *fascicularis*) from the east coast of Malaysia near Kuantan (Garnham, 1959), was used as the laboratory parasite model for these studies. *Anopheles letifer* from the swamp forest study area, located on the opposite side of the main Malaysian mountain range from the B strain type locality of *P. cynomolgi,* were exposed to experimental infections. Oocyst development was poor and no sporozoite differentiation was seen. These results seemed to preclude the involvement of *A. letifer* in the transmission of simian malaria even though this anopheline would invade the forest canopy to feed on monkeys. Eventually, the malaria infections in the *A. umbrosus* group of mosquitoes in this environment were attributed to *P. traguli* of the Malaysian mouse deer, *Tragulus javanicus,* (Wharton *et al,* 1963). The *A. letifer* story was, however, not complete. When a strain of *P. cynomolgi* was isolated from the swamp forest study area and exposed to *A. letifer* from the same locality, it was found that sporozoites developed readily in the salivary glands. Such highly specific strain relationships between parasite and mosquito host must, on occasion, be very important in the epidemiology of monkey malaria. It is not known how frequently such specific relationships occur, but they could be an important consideration in any area where simian malaria exists in the absence of expected vectors or where expected vectors cannot be specifically incriminated in the transmission.

The epidemiology of simian malaria in the fresh water swamp forest of Malaysia is confused by the high levels of natural mosquito infections with *P. traguli.* It may be, that the same species of anopheline is carrying both simian and mouse deer malaria and it is impossible, so far, to find the former in a mixture so dominated by the latter. At any rate, the vector of simian malaria in this environment remains unknown. It is possible that the monkeys become infected in another area, because troops undergo a fairly constant migratory activity, and forested hills, with potential breeding sites for proven vectors of the *A. leucosphyrus* group of mosquitoes, are never far from any location in West Malaysia. Finally, it should be noted that 20 *A. pujutensis* were trapped in the swamp forest environment but none was found infected. This mosquito is of more than passing interest because it is a member of the *A. leucosphyrus* group in which 3 species are proven vectors of simian malaria in Malaysia.

Primary Rain Forests. The rain forests of Southeast Asia occupy hill areas over parts of Indochina, Thailand, Burma, Malaysia, Indonesia, and the Philippines, and all of these areas have certain biological features in common. All support populations of non-human primates, and, wherever investigations have been carried out, non-human primate malarias have been found. A typical high canopied rain forest, in a mountainous area approximately 20 miles north and east of Kuala Lumpur, was selected as a site for the investigation of the transmission of simian malaria.

Mosquito trapping activities in the canopy, with monkey bait, and on the ground, with human bait, produced small catches both in number of individuals and number of species represented. However, 2 species of anophelines, *A. balabacensis introlatus* and *A. leucosphyrus,* were attracted to monkeys in the canopy and to man on the ground. Thus, 2 possible mosquito liaisons between the malaria parasites of man and monkeys had been found. It also seemed significant that both of these species belonged to the *A. leucosphyrus* group. Members of this species complex were known to be primarily jungle breeders, and had been seriously incriminated as vectors of human malaria in parts of North Malaysia, Thailand, Cambodia, Indochina, Burma, and Borneo. Specimens of both species, with sporozoite positive salivary glands, were collected at the rain forest site. The sporozoites from the naturally infected *A. b. introlatus* produced an infection of *P. inui* when inoculated intravenously into malaria-free rhesus monkeys (Wharton *et al,* 1962). Using similar techniques, a naturally infected *A. leucosphyrus,* trapped in the same area, was found to harbor an infection with *P. cynomolgi* (Eyles *et al,* 1963).

The fact that 2 members of the same species complex were vectors of simian malaria was particularly interesting when it was considered that other species, in the same group, were believed to transmit human malaria in areas where simian malaria was found, also. Studies to investigate the possibility that a single species might be responsible for the transmission of both simian and human malaria, in the same environment, were undertaken in a forest area of Cambodia where the local authorities had experienced serious difficulties in trying to prevent transmission of human malaria by using chloroquinized salt and/ or residual insecticides. *Anopheles balabacensis balabacensis* was believed to be important in the transmission of human malaria in the area. These investigations revealed that in that area of Cambodia, *A. b. balabacensis* is predominatly a forest mosquito, attracted to monkeys in the canopy and to man on the ground. Sporozoites from 13 wild caught mosquitoes were inoculated into malaria-free rhesus monkeys, but no infections were produced. Some of the naturally infected mosquitoes were collected in deep forest areas believed to be considerably beyond flight range from the human habitations. The authors concluded that the sporozoites were non-human species (possibly, gibbon parasites) not infective to rhesus monkeys (Eyles *et al,* 1964).

The confirmation of *A. b. balabacensis* as a vector of monkey malaria came as a result of epidemiologic investigations in Northwest Malaysia. In this area, *A. b. balabacensis* was considered to be a vector of human malaria. The study area was a monsoon forest where malaria transmission was believed to be highly seasonal. Rainy and dry seasons occupied approximately equal parts of the year. Sporozoites from naturally infected mosquitoes, trapped in the forest, produced *P. cynomolgi* and *P. inui* infections in malaria-free rhesus monkeys (Cheong *et al,* 1965).

Mangrove Forests. Early in the studies, it was realized that some of the largest monkey populations lived in the extensive mangrove forests along the coast. Actually, it was in this habitat that *M. fascicularis* acquired one of its many local sobriquets, i.e., the crab-eating macaque. Samples of blood from members of a typical troop at Rantau Panjang, near Klang, on the west coast of Malaysia, revealed that these animals did indeed harbor malaria infections. Investigations to determine the vector of the monkey malaria were immediately successful. An *A. hackeri,* collected at the base of a nipah palm during a daytime-resting catch, was found to have sporozoite positive salivary glands. The sporozoites produced a *P. knowlesi* infection following inoculation into a malaria-free rhesus monkey (Wharton and Eyles, 1961). Further elaboration of this discovery proved frustrating. Sentinel monkeys, placed in cages near the mosquito daytime resting sites and breeding areas, failed to become infected. Night-time trapping with both human- and monkey-bait were singularly unsuccessful. *Anopheles hackeri* continued to be plentiful and monkeys were seen whenever the area was visited. Captured *M. fascicularis* were always infected and 29 percent of the leaf-eating langur monkeys *(Presbytis* sp.) carried malaria parasites, too (Wharton *et al,* 1964). Transmission continued to occur because infected mosquitoes were still found at the resting sites. Still, no *A. hackeri* came to any type of primate bait.

At this juncture, a thorough review of the investigative site and its surroundings was made. The mosquito breeding sites were in cavities in the base of nipah palms left after the fronds had been cut for thatch, a major source of income for the people in the area. The land on which these trees were grown had been reclaimed from a tidal area by the use of a series of low bunds, or dams. Tidal changes are not great along the Straits of Malacca, so these dams did not have to be very high. The area, where the mosquitoes were breeding and resting, had been under cultivation for some 20 years. Rubber trees, and some fruit trees, had been planted among the nipah palms, providing an area of deep shade and high humidity where the rainwater would remain in catchments for long periods.

Monkeys could be seen feeding and moving about in this cultivated area during the day but toward the evening they moved to the tidal mangrove forest, a distance of some 500 yards, for the night. Platforms were constructed in the mangrove trees on the tidal side of the bund and equipped with monkey-baited net traps; *A. hackeri* were caught the first night. An extensive search failed to locate mosquito breeding sites other than those previously described, i.e., the bases of the nipah palms, several hundred yards from the trapping area. This enigma was finally clarified when marked mosquitoes *(A. hackeri),* released near the breeding and resting sites, moved purposefully, within a few hours, to monkey-baited net traps in the tidal mangrove.

Ultimately, *A. hackeri* was proven to be a natural vector of *P. coatneyi, P. cynomolgi, P. inui,* and *P. fieldi* as well as *P. knowlesi* (Warren and Wharton, 1963). These species of plasmodia all produce chronic long-lasting infections in the local monkeys and the density of *A. hackeri* did not apparently vary greatly from one time of the year to another. This mosquito is a member of the "jungle breeding" *A. leucosphyrus* group of mosquitoes. Its normal habitat is in the primary hill forests where it breeds in hollow logs and fallen bamboo. The man-made environment near Rantan Panjang had provided a suitable breeding site for the mosquito and there were plenty of monkeys to satisfy their predilection for simian blood. However, a certain amount of adaptation was necessary, for the mosquitoes had to fly a considerable distance, from their fresh-water breeding site, in order to feed on the sleeping monkeys. The adaptation was successful because 5 species of malaria were identified from the area and, as previously noted, 100 percent of the *M. fascicularis* examined from the area were found infected.

Finding this "transmission laboratory" in a man-made environment demonstrated several pertinent points about the ecology of simian malaria in Malaysia. The primate-*A. leucosphyrus* group association is old and apparently highly evolved. It emerges when the two prime elements are combined even in a highly artificial situation. Not only do members of this species complex transmit a variety of simian malarias, but *A. balabacensis balabacensis* is virtually a universal vector. In short, this monkey malaria-mosquito system is flexible as demonstrated by its ability to function in a variety of habitats under numerous environmental stresses.

The most recent studies on the ecology of simian malaria in Southeast Asia were also conducted in West Malaysia. This project was specifically designed to investigate the epidemiology of the first reported natural infection of man with a simian malaria (Chin *et al,* 1965). The infection with *P. knowlesi* had apparently been contracted in a jungle area of Central Malaysia. In 1970, Warren *et al* reported the results of studies in the jungle, where the human *P. knowlesi* infection was probably acquired, and in nearby villages. Human-baited net traps were operated in a village near the forest and on the forest floor. Monkey-baited net traps were maintained on a series of platforms constructed in the forest canopy. Total mosquito collections were augmented by bare-leg catches. Two familiar members of the *A. leucosphyrus* group, *A. leucosphyrus* and *A. b. introlatus,* were caught in both human- and monkey-baited jungle traps, but neither species was found to invade the village. *Anopheles maculatus* was collected in both village and jungle traps but in such small numbers that it did not seem seriously involved in the transmission of monkey malaria to man.

The forested hill on which these studies were conducted was surrounded by swamp forests and some *A. letifer* were collected from the monkey-baited canopy traps reviving the old enigma of the relationship between this mosquito and the transmission of monkey malaria in nature.

The investigators concluded, that the *A. leucosphyrus* group of mosquitoes were essentially primate feeders. Since most of the species are forest dwellers and breeders, they maintain a high level of endemic malaria among the non-human primates and are quite prepared to transmit the same parasites to man if he enters the jungle under appropriate circumstances. It seemed highly likely that this was the manner in which the natural human infection with *P. knowlesi* was acquired. Since the *A. leucosphyrus* group mosquitoes do not leave the forest, in this particular area, at least, there is little or no opportunity for the routine introduction of simian malarias into nearby human populations. However, the chances of man becoming involved with these simian malarias is much greater in areas where the *A. leucosphyrus* group of mosquitoes is represented by *A. b. balabacensis* which maintains the jungle breeding activities of the group but also readily invades villages to feed on man.

Little is known about the epidemiology of simian malaria in the remainder of Asia, but the experience in Malaysia indicates that the presence of *A. leucosphyrus* group mosquitoes is essential. The map, Figure 2, shows the approximate distribution of this species complex in Southeast and South central Asia. Generally, the known distribution of monkey malarias in Asia closely follows the distribution of these mosquitoes. Particular note should be made of the discontinuous distribution in India. Initially, it was thought that the Indian rhesus monkey was free of malaria. It was soon discovered, however, that those trapped in Assam and eastern parts of East Pakistan were sometimes infected and, therefore, unsuitable for malaria research as non-infected animals. In contrast, thousands of *M. mulatta* from central, northern, and western India have been examined, and no infections have been found. We believe, the explanation for this phenomenon lies in the distribution of *A. leucosphyrus* mosquitoes (see map, Fig. 2). They are conspicuously absent from central, northern, and western India, but present in Assam and parts of East Pakistan. The representative of this species complex in southern India and Ceylon, where simian malaria is quite common, is *A. elegans* which we predict will be identified as a natural vector of simian malaria in that area.

Other ecological and epidemiological factors obviously enter into the distribution of the simian malarias in Southeast and South-central Asia. For example, *P. knowlesi* is highly pathogenic to *M. mulatta,* following a rapid and almost invariably fatal course. Therefore, without severe modifications on one or both sides, this parasite and the monkey could not survive in the same area. There are probably other malaria parasites which develop readily in a limited range of hosts. There are, for example, strains of malaria in Malaysian leaf monkeys *(Presbytis* sp.) which grow only with

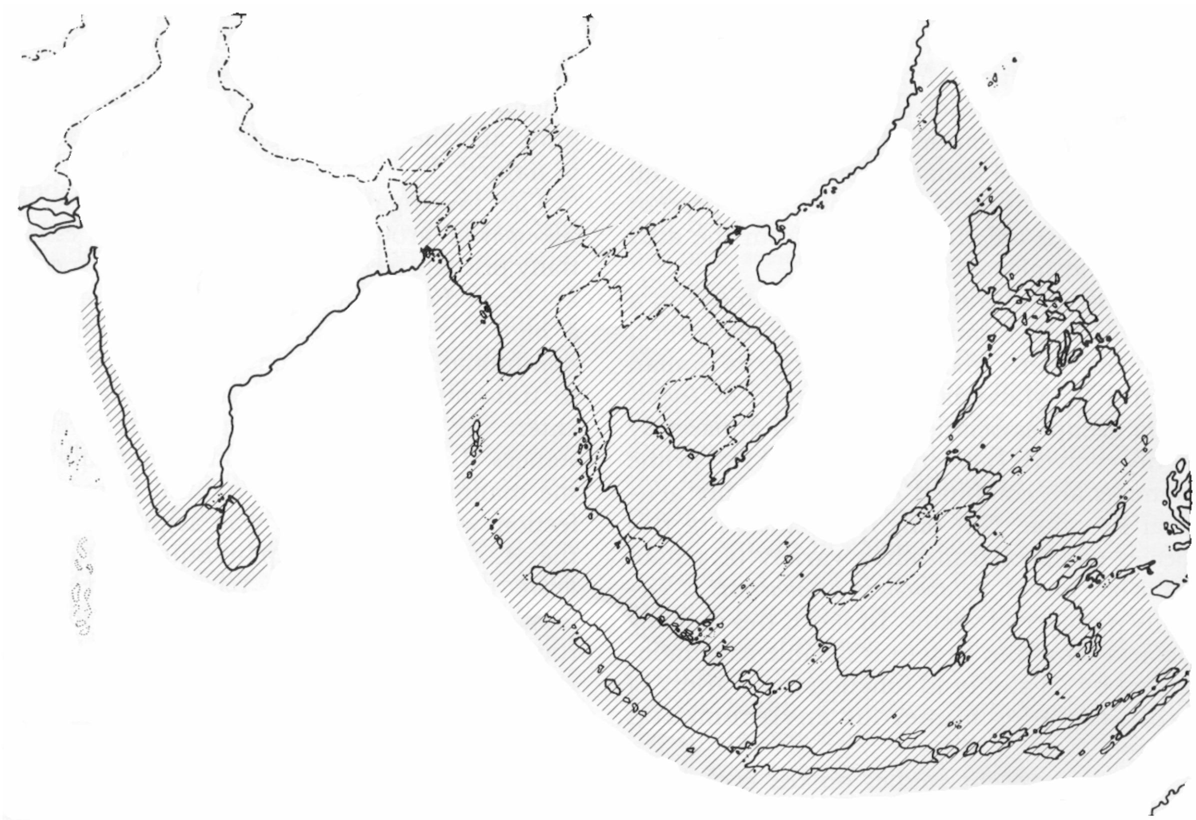

FIGURE 2.—Approximate distribution of *Anopheles leucosphyrus* group mosquitoes in Southeast and Southcentral Asia (modified from Colless, 1956).

difficulty in *M. mulatta* (Eyles *et al,* 1962). However, these factors do not seem to contribute to the distribution of the parasite at the same level as the limitations imposed by the vector characteristics. The correlation between malaria parasite distribution and the distribution of the *A. leucosphyrus* group mosquitoes is apparently due to feeding preferences and biting habits of the vectors rather than the susceptibility of the mosquito to the parasite. Experimentally, the simian malarias from Southeast Asia can be transmitted by a large number of mosquito species (Warren and Wharton, 1963; Warren *et al,* 1963; Collins *et al,* 1965, 1966, 1967, 1967a, 1968, 1968a; Collins, 1969). In addition, it seems probable that in local situations, highly specific relationships may have evolved, and mosquitoes, other than members of the *A. leucosphyrus* group, may be involved. *Anopheles letifer,* in fresh water swamp forests in Malaysia, is a prime candidate for such a role. However, it is our opinion that the relationships between simian malaria and the *A. leucosphyrus* group mosquitoes is so intimate that future extensions in the geographic distribution of the simian malarias in Southeast and South central Asia will be associated with established populations of one or more members of this mosquito species complex.

AFRICA

Information currently available on the epidemiology of non-human primate malaria in Africa is limited. Three species of *Plasmodium* have been described from the great apes of Africa, one of which may be shared with man *(P. rodhaini).* The other 2 species, *P. reichenowi* and *P. schwetzi* are closely related to the human *P. falciparum* and *P. vivax-P. ovale* stocks. Only one true malaria parasite has been reported from African monkeys, *P. gonderi,* although the related genus, *Hepatocystis,* is common in these animals.

We are not aware of any studies that have been specifically directed toward identifying the natural vectors of the ape and monkey malarias in Africa. Gillies and De Meillon (1968) in their comprehensive work on the anophelines south of the Sahara do not record any species naturally attracted to non-human primates. Garnham (1951) used monkeys as bait in his studies on the natural history of simian hepatocystis in Uganda. Platform and ground traps were used. Two *A. coustani* and 8 *A. implexus* were caught; the author did not record whether these came from ground or from platform traps. The paucity of information available on the natural attraction of African non-human primates for anophelines is surprising considering the interest of many workers in the possibility that man and chimpanzees shared their malaria parasites, and that the apes might well serve as reservoirs for human malaria. Eventually, one species, *P. malariae,* was said to exist naturally in both man and the chimpanzee. Still, there was no concerted effort to determine which mosquitoes were responsible for maintaining the infections in the apes, nor if such vectors were prone to feed on man as well.

There is scant information on the experimental susceptibility of a variety of anophelines to malaria parasites of African apes and monkeys. However, most of the work was carried out in Europe and the United States; the species of mosquitoes involved were not African. Bray (1957) fed *A. gambiae* on chimpanzees infected with *P. reichenowi* and reported gut infections; the salivary glands did not become positive. The same investigator, (Bray, 1958) succeeded in transmitting *P. schwetzi* with *A. gambiae,* but no sporozoites were seen in the inoculum. He concluded, that this mosquito would be a poor natural vector since the sporozoites survived only a short time in the salivary glands. *Anopheles gambiae* were also shown to be refractory to at least one strain of *P. malariae* isolated from the chimpanzee (Bray, 1960).

There is no information available on possible vectors of *P. gonderi.* There are a great number of species of anophelines in Africa that are strictly forest breeders and biters but information on host preferences is too incomplete at present to allow for speculation on their possible role in the transmission of non-human primate malaria.

Likewise, there is no information available on either natural or experimental vectors of the two malaria parasites described from Madagascan lemurs (*P. girardi* and *P. lemuris*).

AMERICA

Information on the epidemiology of non-human primate malaria in the monkeys of South and Central America is more complete than for Africa. Deane and his colleagues in São Paulo have been studying the distribution and epidemiology of the simian malarias in Brazil for a number of years. The results of ground and platform mosquito catches, using monkey-bait, implicate the bromeliad breeding *A. cruzi* as the mosquito responsible for the holoenzootic status of *P. simium* in Horto Florestal da Cantareira near São Paulo. Similar results were obtained in other study areas in southeastern Brazil (Santa Catarina and Espiritu Santo) (Deane *et al,* 1969).

The situation becomes more complex in Amazonas where a greater variety of mosquitoes invade the canopy to feed on monkeys. At Porto Maria, where only one monkey was found to be parasite positive, a variety of anophelines were found feeding in or near the canopy; *A. mediopunctatus* being particularly numerous. The investigators felt that these mosquitoes were probably not important in the transmission of monkey malaria since the same species was found in other areas where infections in monkeys were nil. We would suggest that such areas should be monitored regularly, because the simian malarias of South and Central America are still in the process of extending their host and geographic range. The argument, that a given species of anopheline is probably not involved in malaria transmission, because it is abundant in an area where no vertebrate infections occur, may be debatable since it is likely that all Western Hemisphere anophelines existed for thousands of years in the absence of malaria.

Two species in the subfamily Anophelinae, *Anopheles neivai* and *Chagasia bonneae,* were found to be attracted to monkeys consistently in the forest canopy near Manaus, and Deane *et al.* (loc. cit.) felt that these species were probably responsible for the transmission of *P. brasilianum* in that area. There is less information available on the vectors of *P. brasilianum* in other parts of South and Central America. Galindo *et al* (1950), working in Panama, trapped mosquitoes, with human bait, on the ground and on platforms, at various levels, in the forest canopy. A variety of anophelines were caught, but no single species was present in large numbers. They found *A. neivai* in the forest canopy, in an area near Panama City; a species Deane *et al.* (loc. cit.) considered a probable vector of *P. brasilianum* in the Manaus area. Undoubtedly, new information on the epidemiology of simian malaria in Central America will be available soon, for this subject is now under investigation by Young and his colleagues at the Gorgas Memorial Laboratory in Panama.

There is not enough information available to allow for speculation on the influence of epidemiological factors on the distribution and prevalence of simian malarias in the Western Hemisphere. *Plasmodium brasilianum* has adapted well to a variety of genera and species of monkeys from southeastern Brazil to the jungles of Panama and, possibly, even further north. During the same period, *P. simium* has remained confined to an area of southern and eastern Brazil. However, we are of the opinion that there are many anophelines in the jungles of South America capable of transmitting *P. simium,* and the limits in its present distribution are due to a lack of movement, after a recent introduction into an exotic environment; rather than to failure in many areas due to an unreceptive transmission system. Under such circumstances, it is possible that in areas where the sub-human primates are now negative for malaria, future investigations will reveal infections in the same primates. Therefore, we believe that the host(s), geographic distribution, and aspects of vector limitations of the simian malarias in South and Central America will remain confusing, unstable, and subject to change until the parasites have tested all environmental niches in the available vertebrate and invertebrate hosts.

It would be convenient, if investigators of simian malaria ecology in Africa and South America were able to find a correlating factor as specific as the *A. leucosphyrus* group of mosquitoes seems to be in Asia. However, as pointed out earlier, the relationship between the simian malarias of Southeast and South-central Asia and the *A. leucosphyrus* group of mosquitoes is probably a very old and highly evolved one. It is our belief, that the primate plasmodia have been living in Africa for a shorter period than in Asia and are only recent arrivals in the New World. Therefore, it would seem that the chances of finding a single species complex of mosquitoes, south of the Sahara, responsible for the transmission of non-human primate malarias, is unlikely and the opportunity for such a specific relationship to have developed in Central and South America is dim indeed.

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