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Author: CONTACOS, PETER G.

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Primate Malarias: Man and Monkeys

PETER G. CONTACOS

Section on Primate Malaria
Laboratory of Parasitic Diseases
National Institute of Allergy and Infectious Diseases
National Institutes of Health
P.O. Box 80190
Chamblee, Georgia 30341

Abstract

The question whether malarias of animals could be considered true zoonoses was examined. The research in this connection for the past decade or so was reviewed. That simian malarias are true zoonoses has been adequately demonstrated. In addition, there is great potential for human malarias being true anthroponoses. The author considers, therefore, that the significance of non-human reservoirs of human malaria in the control or eradication of malaria should be reconsidered.

The question as to whether malarias of animals could be considered true zoonoses has been of interest for many years. We have known for some time that malarias of some non-human primates could infect man, but only when exposure to infection was by the inoculation of parasitized blood; i.e., asexual erythrocytic parasites.[1-4] Under these conditions, however, the malarias of animals could not qualify as zoonotic since infection by natural means is by the bites of infected anopheline mosquitoes. The few attempts to infect man with simian malarias by mosquito bite had always failed.[5-7] Because of this, the malarias of animals were not considered to be an important hazard in the planning for a program of malaria eradication. In fact, at the World Health Assembly in 1955, no consideration was given to non-human primate malarias as being a problem in or posing a threat to the world-wide eradication of malaria. To repeat, this was due to the fact that there were no documented infections by natural means.

Five years later, however, the first infection of a human with non-human primate malaria, initiated by the bites of mosquitoes, occurred in the late Dr. Don Eyles.[8] This infection was with the B strain or subspecies *bastianellii of Plasmodium cynomolgi,* a vivax-like parasite of macaques. At about the same time, three other persons working with this parasite in other laboratories also became infected accidentally, again by bites of heavily infected mosquitoes. The parasite was then immediately established in volunteers and studied intensively at our Malaria Project at the U.S. Penitentiary in Atlanta, Georgia and at the National Institutes of Health in Bethesda, Maryland.[8-12]

Since 1960, a total of 7 species of monkey malaria have been reported as transmissible to man by natural means, that is by mosquito bite; namely, *P. cynomolgi,*[8,13,14] *P. brasilianum,*[15] *P. eylesi,*[16] *P. knowlesi,*[17,18] *P. inui,*[19] *P. schwetzi*[20] and *P. simium.*[21] Four of these species are from Asia; three *(cynomolgi, knowlesi, inui)* naturally infect macaque and langur monkeys and *eylesi* naturally infects the gibbon. Two of these species are from the New World; *brasilianum* naturally infects spider

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(Ateles sp.), capuchin *(Cebus* sp.) and howler (*Alouatta* sp.) monkeys while *simium* naturally infects the howler and woolly-spider monkeys. *Plasmodium schwetzi* is found in Africa naturally infecting the chimpanzee and gorilla.[22]

In our studies on simian malarias in man, at the Unit on Human Malaria in Atlanta, over 100 infections with 7 different strains or isolates of *P. cynomolgi* have been established experimentally in volunteers. In addition, there have been 25 human infections with *P. brasilianum,* 11 infections with *P. schwetzi,* 7 infections of the OS strain or subspecies *shortti* of *P. inui,* and 20 infections with *P. knowlesi.*

Although the experimental transmissions by mosquito bites pointed out strongly that many of the simian malarias were indeed zoonotic, absolute proof required the detection of such infection in nature. This occurred in 1965 when Chin *et al.,*[17] reported a natural infection of *P. knowlesi* that had been acquired by a Caucasian while on assignment in Malaysia. Initially, this infection had been diagnosed as *P. malariae* and was established in one of our volunteers only because of a great need for a strain of human quartan malaria for chemotherapeutic studies. This parasite, however, once established in our volunteer, had a quotidian periodicity which meant it had to be *P. knowlesi.* Subinoculation into a rhesus monkey confirmed its identity as *P. knowlesi.* The parasite was subsequently transmitted by mosquito bites from monkey to monkey, from monkey to man, from man to man, and from man back to monkey.[18] Except for the fact that we required several isolates of quartan malaria, this zoonotic infection would have slipped by unnoticed. One wonders how many other such infections are confused with human malaria.

A possible second infection of man in nature with a monkey malaria in Brazil *(P. simium)* was reported by Deane *et al.* in 1966.[21] Using a strain of *P. simium* sent to us by Dr. Deane, we have consistently failed to infect man in several attempts under controlled conditions. It is possible a different isolate would infect man. We hope to receive several other isolates of this species in the near future for additional attempts to confirm this report.

Infections of simian malaria in man can be relatively mild to rather severe at times, depending upon the species of monkey malaria. The quartan type parasites, *P. brasilianum* and *P. inui,* usually produce infections which are very mild in man compared to their human counterpart, *P. malariae. Plasmodium cynomolgi,*[10] *P. schwetzi*[20] and *P. knowlesi,*[18] all produce clinical disease in man which generally varies from mild to moderate compared to that seen in their human counterparts; but, may rarely be severe such as in the case of *P. knowlesi.* The striking feature of cynomolgi monkey malaria infections in man is the high degree of clinical manifestations observed in relation to the low level parasitemias of these infections.

Generally, the parasitemias are of a much lower density than what is observed in the natural or monkey hosts. Duration of parasitemia can be long ranging from 10 to 169 days. Clinically, a number of these species can produce in man clinical manifestations not unlike those seen with some of their human counterparts; namely, headache, nausea with or without vomiting, chills, and fevers up to 106°F. Hepatosplenomegaly with or without tenderness is common. However, all are generally self-limiting with spontaneous cure without antimalarial therapy. Rarely, the severity of a knowlesi malaria infection in man has dictated intervention with antimalarial drug.

Now, I would like to turn our attention to the reverse phenomenon of zoonosis; that is, human malarias in non-human primates, a possible anthroponosis.

Up until recently, the only non-human primates that could be experimentally infected with human malaria parasites were the anthropoid apes: the chimpanzee *(Pan satyrus)* and the white-handed gibbon *(Hylobates lar).* The chimpanzees are susceptible to all 4 species of human malaria.[23] To date, the gibbon has been found to be susceptible to only falciparum and vivax malarias.[24-27] In 1966, Cadigan *et al.,*[28]

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reported infection of splenectomized pig-tailed and long-tailed macaques by the direct inoculation of human blood parasitized with falciparum malaria. In addition, splenectomized rhesus monkeys could be infected with falciparum malaria once it had first been established in the gibbon. All the above mentioned primates are indigenous to the African and Asian continents.

The first report of an experimental human malaria infection of *P. falciparum* in New World monkeys was that of the Taliaferros[29] in 1934. They indicated that such infections were low grade, transitory and of very short duration. No further studies were conducted with New World monkeys in this regard until just recently, when a number of monkeys indigenous to the American continent have been found capable of supporting infection with 3 of the 4 human malarias; namely, vivax,[30-32] falciparum,[33,34] and malariae[35,36] malaria. These monkeys include the owl or night monkey *(Aotus trivirgatus)*, the titi marmoset *(Saguinus geoffroyi)*, the squirrel monkey *(Saimiri sciureus)*, the capuchin *(Cebus capucinus)*, the black howler *(Alouatta villosa)*, and the black spider monkey *(Ateles fusciceps)*. All, except for the capuchin, howler and spider monkeys, can be infected directly with at least one of the human malarias by the inoculation of parasitized human blood. At present, capuchin,[37] howler and spider monkeys,[38] and the squirrel monkey[39] can be infected with falciparum malaria only after the parasite is first established in owl monkeys.

Our studies with the infection of New World monkeys have been chiefly with owl monkeys. We have been able to establish 7 strains of *P. vivax*, 3 strains of *P. falciparum*, and 1 strain of *P. malariae* in owl monkeys. To date, all attempts to establish the 4th human species, *P. ovale*, in these monkeys have failed.

The ease with which several of the human species of malaria have been experimentally established in these "abnormal" simian hosts was indeed surprising. In fact, 6 of the 7 strains of *P. vivax* and 2 of the 3 strains of *P. falciparum* initially established by us in owl monkeys were in intact (non-splenectomized) animals.

The infectivity of the human malaria parasites in owl monkeys to anopheline mosquitoes has been demonstrable in our studies.[40,41] We have been able to transmit 3 species of human malaria (falciparum, malariae, and vivax) from owl monkeys back to man by mosquito bites.[30,42,43] In addition, other investigators have been able to transmit one of the human malarias (vivax) by mosquito bites from owl monkeys to other owl monkeys as well as other non-human primates.[44,45]

It has already been demonstrated that human malaria can be anthroponotic in Old World monkeys (Africa and Asia). What remains to be seen with New World monkeys is whether the human malarias can be transmitted by mosquito bite directly from man to monkeys. If such transmissions can be achieved experimentally in New World monkeys, then human malaria could be anthroponotic in all 3 continents (African, Asian, and American) in which malaria is still a problem. Obviously, the severity of the problem would depend in most part on the degree of cohabitation between man and monkeys as well as the vector potentials and biting preferences of the local anopheline mosquitoes.

In summary, the potential for simian and human malarias being zoonoses and anthroponoses, respectively, has been adequately demonstrated during the past decade. It seems appropriate, therefore, that the role and significance of non-human reservoirs of human malaria in the control and/or eradication of malaria be reconsidered.

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