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MALARIA AS A ZOONOSIS

by

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Introduction

The presence of malaria parasites in various species of monkeys was observed already in 1898 by Koch and a year later Laveran gave the name of "P. kochi" to one species of simian plasmodia. During the first quarter of the present century there was a steady stream of reports on malaria in monkeys imported into zoos from many parts of the world. Most of the early work on simian malaria was done in India where Sinton, Mulligan and their colleagues carried out a series of remarkable studies which provided the basis for subsequent research on the parasitology and chemotherapy of primate malaria.

During the early thirties P. knowlesi isolated in India was experimentally transmitted to man by Knowles and Dasgupta; this plasmodium was quite largely used in Romania for malariatherapy by blood infection. In the late thirties Rodhain in Belgium devoted much attention to malaria of anthropoid apes and showed the close relationship, if not identity, between quartan malaria parasites of apes and P. malariae of man.

A successful attempt to transmit the vivax-like parasite of chimpanzees (P. vivax schwetzi) was also reported by Rodhain. All these studies were carried out by inoculation of parasitized blood.

The importance of studies on simian malaria was brilliantly demonstrated in 1948 by Shortt & Garnham. The discovery of exoerythrocytic stages in the liver of a monkey infected with P. cynomolgi pointed the way for finding a year later the tissue stages of P. vivax of man. The similarity of response of P. cynomolgi of monkeys and P. vivax of man was of immense value for the development of antimalarial drugs.

While the studies of parasites of higher apes were of interest, the observations on the relationship of malaria parasites of lower monkeys to man were of far greater importance with regard to the problem of malaria as a zoonosis.

In May 1960 an accidental discovery by Eyles and his colleagues that P. cynomolgi of lower primates are transmissible to man by mosquitos lead to a tremendous surge of new knowledge of simian malaria. Within five years the number of species and strains of plasmodia of monkeys discovered in Malaya, in India, in Ceylon and in Brazil reached one dozen. Many attempts were made at transmitting several species of simian malaria to man by mosquitos; these experiments confirmed that P. cynomolgi and its subspecies can be transmitted to man through Anopheles with relative ease and that a passage of this infection from man to man and back to the monkey was feasible (Eyles, 1963).

Subsequently it was found that the establishment of the human infection with other simian plasmodia was more difficult but at least two (P. brazilianum and P. inui) were passed into human volunteers by the bites of infected Anopheles.

Thus the possibility of the natural two-way transmission of simian malaria in the human species was established. However, there was no proof that this can actually happen in nature. This proof was provided by the observation made in 1965 of a case of P. knowlesi malaria in a visitor to Malaya, whose infection was detected, identified and subsequently transmitted to volunteers and to rhesus monkeys in the United States of America (Chin et al., 1965).

The second important observation concerned the natural infection of a man with P. simium reported from Brazil (Deane et al., 1966).

The recent finding that the Anopheles leucosphyrus complex which is widely distributed in South East Asia can harbour several species of simian malaria parasites (P. cynomolgi, P. inui) gives some substance to the supposition that zoonotic infections may be possible in forested areas of this part of the world (Cheong et al., 1965).

The parasitological, ecological, entomological and evolutionary aspects of simian malaria were fully discussed at the Symposium on Simian Malaria held in August 1963 at the XVI International Congress of Zoology in Washington and subsequently published in the Journal of Parasitology, 1963, vol. 49, No. 6. The relevant papers consitute the most complete documentation available but the studies carried out during the past three years have expanded our knowledge so fast that an up to date review of the subject is needed. Fortunately two important books on this subject are due to appear shortly. One by P. C. C. Garnham on plasmodia of animals and man will be published by Blackwell before the end of 1966. A monograph on simian malaria by G. R. Coatney and his colleagues is now in preparation and may be completed in 1967.

The First Report of the WHO/FAO Expert Group on Zoonoses (1951) limited this term to "diseases which are naturally transmitted between vertebrate animals and man". The Second Report of the WHO/FAO Expert Committee on Zoonoses (1959) modified the definition which now refers "to diseases and infections naturally transmitted between vertebrate animals and man". The absence of malaria in the list of zoonoses quoted in the Second Report of the WHO/FAO Expert Committee (1959) was understandable as there was no evidence of natural foci of human malaria maintained by an animal reservoir generally and by higher apes and monkeys in particular.

The discovery of the transmission of malaria of lower monkeys to man in 1960 at the time when malaria eradication programmes were gathering momentum, was of sufficient importance to be discussed by the WHO Expert Committee on Malaria (1961). The conclusions of the Report of this Committee were as follows:

> "It might appear that the discovery of the transmissibility to man of some strains of malaria parasites of lower monkeys has uncovered an additional obstacle to the global eradication of human malaria by providing evidence of the possibility of a simian reservoir of infection. Such a conclusion, however, may not be justified. In the present state of knowledge, it seems that malaria, as a zoonosis, is of only limited importance in the global programme of malaria eradication.

"The areas where foci of human malaria could perhaps be maintained from a simian reservoir of infection are few and relatively small in relation to the enormous territories where monkeys either do not exist or are present only in very small numbers, or where simian malaria parasites are absent, or non-infective to man, or not transmissible by those Anopheles that transmit human malaria."

1. Malaria in anthropoid apes

The following table summarizes the known distribution of plasmodia found in higher apes:

Natural host	Plasmodium	Described by	Locality	Human homologue
Pithecus sp. (orangutan)	P. pitheci[1]	Halberstadter & Provazek, 1907	Boneo Sumatra	
Pan sp. (chimpanzee)	P. schwetzi (P. vivax schwetzi)	Brumpt, 1939	Congo, Sierra Leone, Guinea, Liberia, Cameroon	P. vivax
Pan sp. (chimpanzee)	P. (L) reichenowi	Sluiter et al., 1922	Cameroon, Congo, Liberia, Sierra Leone	P. (L) falciparum
Pan sp. (chimpanzee)	P. rodhaini	Brumpt, 1939	Congo, Cameroon, Sierra Leone, Liberia	P. malariae
Gorilla sp. (gorilla)	P. (L) reichenowi	Reichenow, 1917	Cameroon, Congo	P. (L) reichenowi
Hylobates sp. (gibbon)	P. hylobati[2]	Rodhain, 1941	Java, Malaya, Thailand, Borneo	

[1] The exact periodicity of P. pitheci is unknown, but it belongs probably to the tertian group.

[2] P. hylobati has a quartan periodicity, but it is likely that other species of this group of plasmodia will be described. (In fact P. youngi described in 1963 from a gibbon is very close to P. hylobati; it has a tertian periodicity.)

The three homologous parasites of man and chimpanzee are morphologically indistinguishable. Rodhain showed that the quartan parasite which this animal harbours is identical with the human P. malariae and can be transmitted to man by blood infection.

The transmission of human P. malariae to a chimpanzee through the A. gambiae was carried out by Bray in 1959, who demonstrated the presence of pre-erythrocytic forms of this parasite in the liver of the experimental animal.

The human P. vivax was transmitted to chimpanzees in 1956 by Rodhain, who showed that the tissue stages of this parasite develops in the liver of the animal. Bray observed in 1957-1958 the tissue stages of human P. vivax in chimpanzees after transmission through mosquitos including A. gambiae. This author suggested that the benign tertian parasite of man be called P. vivax vivax and the homologous parasite of chimpanzees: P. vivax schwetzi. The human P. ovale was transmitted in 1957 by Bray to a chimpanzee through A. gambiae; pre-erythrocytic stages of P. ovale were found in the liver of the experimental animal.

The morphology of P. reichenowi of Liberian chimpanzees was studied by Bray who concluded that this parasite is not identical with the human P. falciparum. Both species belong to the subgenus Laverania (L.) proposed by Bray on account of their differences from the genus Plasmodium.

The infection of A. gambiae by P. (L.) reichenowi was not successful but P. falciparum of man was transmitted to chimpanzees by intravenous inoculation of sporozoites of infected A. gambiae. It seems that P. falciparum will grow in the chimpanzee's liver but the erythrocytic infection of the animal can take place only if it is splenectomized.

The present situation with regard to the relationship between malaria parasites of man and higher apes could be summarized as follows:

Plasmodia of anthropoid apes that show a close relationship with human malaria parasites are limited to a relatively small part of West and Central Africa. Plasmodia of Far Eastern anthropoid apes are less closely related to human malaria parasites (Bray, 1963).

The parasites of African anthropoid apes are virtually indistinguishable from the three main species infecting man. In the case of falciparum-reichenowi parasite attempts to infect chimpanzee from man have been more successful if the animal was splenectomized. In the case of the vivax-schwetzi parasite the human plasmodium produced in the chimpanzee an asymptomatic infection; the chimpanzee plasmodium produced in man a mild and transient infection. Man proved to be most susceptible to the infection with the malariae-rodhaini parasite of the chimpanzee which produced febrile symptoms with quartan periodicity and was carried through several human blood passages; the infection of chimpanzees with the human strain was symptomless with scanty parasites. The situation with regard to the human ovale malaria is similar to that of the vivax-schwetzi plasmodium.

The concept of malaria of higher primates as a zoonosis is certainly valid though its confirmation of its presence in natural conditions is difficult; its practical importance, seen from the medical and public health angle, is very slight.

2. Malaria parasites of lower monkeys

Garnham's (1963) useful classification of this series of species of simian plasmodia is as follows:

(1) "Quartan group" with quartan periodicity, producing light stippling of the erythrocytes and undergoing a lengthy sporogony and exoerythrocytic schizogony (P. inui, P. brasilianum, P. hylobati, P. shortti).

(2) "Ovale group" with tertian periodicity, producing heavy stippling of the erythrocyte (P. simium, P. fieldi).

(3) "Gonderi group" with tertian periodicity, producing light stippling of the erythrocytes (P. gonderi, P. coatneyi).

(4) "Benign tertian group" with tertian periodicity, producing Schuffner's dots in the erythrocytes (P. cynomolgi, P. c. bastianellii, P. c. cyclopis).

(5) "Quotidian group" with daily periodicity, producing stippling of the erythrocytes and undergoing rapid exoerythrocytic schizogony (P. knowlesi).

The classification of Contacos & Coatney (1966) is slightly different: these authors distinguish the following groups: (1) Vivax type (P. cynomolgi, P. cynomolgi bastianellii, P. cynomolgi cyclopis, P. gonderi, P. schwetzi, P. simium); (2) Malaria type (P. inui, P. brasilianum, P. hylobati); (3) Falciparum type (P. reichenowi, P. coatneyi); (4) Ovale type (P. fieldi); (5) Quotidian type (P. knowlesi). (This classification includes some plasmodia of higher apes).

The following table based on Garnham's classification gives a tentative summary of the present position with regard to the main malaria parasites of lower monkeys. The table does not quote the name of first or subsequent authors who discovered or re-described this series of parasites. Most of the pre-1964 information will be found in the "Symposium on simian malaria" (Journal of Parasitology, 1963, vol. 49, No. 6). Because of the uncertain taxonomic classification and nomenclature of a number of lower monkeys only generic names of some natural hosts are given, together with the common name.

This table is self-explanatory and indicates that out of about ten known species or species complexes of malaria parasites of lower monkeys at least four can be transmitted to man by blood infection, and five by mosquito bites. Truly natural transmission of infection by mosquitos has been reported in three simian species, though in every case it has been limited to one or a few individuals.

Nevertheless, and in spite of the increasing evidence of the closer than previously suspected host-parasite relationship concerning malaria parasites of lower monkeys and man it seems that simian malarian man is a relatively rare occurrence and that the importance of malaria as a zoonosis should not be exaggerated.

Even if there are small foci of simian malaria in some parts of the world where the contact between monkeys and the human population can be maintained through forest mosquitos it is more than doubtful that this will consitute a problem for malaria eradication since such cases will be either exceptional or at the most limited to a few sporadic infections.

The validity of this argument could be confirmed by a recent unsuccessful attempt to isolate strains of simian malaria from a large sample of aboriginal population in Malaya where simian malaria is exceedingly common.

TABLE 1 : MALARIA PARASITES OF LOWER MONKEYS

Group (acc.to Garnham)	Species of plasmodium	Original hosts	Country	transmission to man by: blood	transmission to man by: mosquito	Remarks
Benign tertian group	P. cynomolgi s.l. P. cynomolgi bastianellii P. cynomolgi cyclopis P. cynomolgi ceylonensis	Macaca irus (long-tailed macaque) M. nemestrina (pig-tailed macaque) M. radiata M. mulatta (rhesus) M. cyclopis M. sinica (toque monkey) Presbytis cristatus (leaf monkey) P. cutellus (grey langur)	S. India, East Pakistan Taiwan, Philippines, Malaya, Java, Cambodia, Ceylon	+	E + N?	Passage back to monkey achieved by mosquito. Isolated from A. hackeri, A. balabacensis introlatus, A.leucosphyrus
Quartan group	P. inui incl. P. inui shortti	Macaca irus M. nemestrina M. radiata M. mulatta M. cyclopis M. sinica Cynopithecus niger Presbytis sp.	India, East Pakistan, Thailand, Viet-Nam, Taiwan, Philippines, Malaya, Borneo, Sumatra, Sulawesi, Ceylon	+	E +	P. inui shortti is identical with P. osmaniae isolated in South India. Isolated from A. hackeri A. leucosphyrus, A. balabacensis
Quartan group	P. brasilianum	Brachyurus calvus (cacajao) Ateles sp. (spider monkey) Cebus sp. (capuchin monkey) Alouatta sp. (howler monkey) Lagothrix sp. (woolly monkey)	Brazil, Panama, Mexico , Peru	+	E +	Passage back to monkey by blood
Quotidian group	P. knowlesi incl. P. knowlesi edesoni	M. irus Presbytis sp. (leaf monkey) M. nemestrina	Philippines, Taiwan, Malaya, Java	T +	N +	P. knowlesi isolated in nature from A. hackeri in Malaya
Gonderi group	P. coatneyi	M. irus	Malaya, Philippines	-	-	Isolated from A. hackeri in nature in Malaya
Gonderi group	P. gonderi	Cercocebus sp. Cercocebus fuliginosus (mangabey) Mandrillus sp. (drill)	Congo, Cameroon, Liberia	-	-	Former "P. kochi"
Ovale group	P. fieldi	M. nemestrina	Malaya	-	-	Isolated from A. hackeri and A. balabacensis introlatus
Ovale group	P. simium	Alouatta fusca (howler monkey)	Brazil	-	N +	Probable vector : A. (K.) cruzi
Ovale group	P. simiovale	M. sinica	Ceylon	-	-	Tertian periodicity; affinity with P. ovale, P. fieldi, P. simium
	P. fragile	M. sinica sp	Ceylon	-	-	Corresponding to the New Nilgiri parasite found in India in Macaca radiata; close to P. coatneyi

Note : 1. Only successful transmission of these parasites to man is indicated. E stands for experimental infection; T - for therapeutic malaria and N - for natural or presumably natural infection.

2. Parasites of other primates (such as lemur) are not included in this list. At least two new parasites of monkeys have now been discovered in South East Asia and the reports are in preparation.

3. Infection of monkeys by human plasmodia

Research on human malaria has been handicapped from the start by the absence of experimental animals susceptible to plasmodia of man. Much scientific progress in parasitology of malaria was due to the use of avian, rodent and simian malaria.

Attempts to transmit human malaria parasites to monkeys and apes were made by several workers (Taliaferro, Rodhain, Sinton, Mulligan, Garnham, Bray). It appeared that splenectomized chimpanzee was the relatively best species for these studies (especially on P. malariae) though the use of this expensive animal was obviously limited.

Recent progress in this field indicates, surprisingly enough, that not only chimpanzee but also other apes and especially lower monkeys may harbour and develop both P. falciparum and P. vivax.

Blood infection by drug resistant P. falciparum from Malaya (Camp strain) was induced in splenectomized chimpanzees using sporozoites (transmitted by A. quadrimaculatus) or parasitized human and chimpanzee blood. Five serial blood passages were successfully completed (Hickman et al., 1966).

Successful experimental blood-induced infections with human P. falciparum from Thailand were obtained in splenectomized gibbons (Hylobates species) and serial blood passages were carried out (Ward et al., 1965).

Moreover the same group of authors has just reported from Thailand that the splenectomized gibbon is susceptible to sporozoite - induced infection of P. falciparum transmitted by A. balabacensis (Gould et al., 1966).

Not less interesting is the report by Porter & Young (1966) who have infected two species of Panamanian monkeys with P. vivax. The night monkey (Aotus species) has shown great susceptibility to this human parasite and is a promising host for further studies. Serial transmission through A. albimanus was successful. It also appears that P. vivax has been transmitted by blood infection to the Brazilian howler monkey.

Finally it has been shown quite recently by Cadigan et al. (1966) that P. falciparum obtained from a Thai woman and transmitted by blood infection to a splenectomized gibbon could be re-transmitted from this higher ape to a splenectomized Macaca irus. There was no evidence of clinical symptoms in the animals. Further studies revealed that a direct transfer of human P. falciparum to splenectomized Macaca mulatta (rhesus) and to M. nemestrina (pig-tailed monkey) was also possible. The fact that Macaca irus which is a prolific monkey, easily adapted to colonization can be infected with human P. falciparum is of considerable importance, though it is too early to assess the value of such an animal for extensive parasitological, immunological or chemotherapeuric studies on human malaria.

These results coupled with the events of the previous years which showed that P. knowlesi can infect man and that P. cynomolgi, P. inui, P. brazilianum and P. simium can be transmitted to man with relative ease are not only of practical value but also of considerable interest to those who believe that they may explain the evolutionary basis of some zoonoses.

As pointed out by Garnham (1966) two simian plasmodia of the New World: P. simium (which resembles P. ovale) and P. brazilianum (which resembles P. malariae) infect man and this may be explained by the hypothesis that these two human species were brought to the New World by man relatively recently and eventually got adapted to the local monkeys. However, the evolutionary pattern of the primate plasmodia is still puzzling and no coherent picture of it can be presented (Bruce-Chwatt, 1965).

4. Entomological aspects of transmission of simian malaria

In the incrimination of the main vectors of human malaria the dissection of wild caught Anopheles for the presence of oocysts or sporozoites has always played an important part. The sporozoite infection has usually been regarded as a convincing proof that the species concerned is involved in the transmission of human malaria though it was known that some anopheline species not normally found near houses may be vectors of animal malaria. During the past few years an increasing amount of information on the behaviour of mosquitos and on the transmission of animal malaria showed that many Anopheles can be vectors of several species of plasmodia. The tabulated information on Anopheles as vectors of malaria parasites of animals prepared by Bray & Garnham (1964) indicated that 23 anopheline species were proven or suspected natural vectors of animal malaria and 25 anopheline species as experimental vectors. This information limited to proven or most probable vector of simian malaria and modified according to more recent data is given in Table 1.

It is certain that the table is incomplete as it does not contain the very recent and unpublished information. Many more colonized Anopheles species have been successfully used for experimental transmission of plasmodia of primates from monkey to man (P. cynomolgi, P. brazilianum, P. inui, P. knowlesi) or from man to apes and monkeys (P. vivax) (Warren & Wharton, 1963).

It is obvious that the previous interpretation of the vectorial importance of Anopheles based on the sporozoite rate found in nature should be revised and related to the criterion whether the plasmodial infection is of human or animal origin. The full importance of this problem has now become obvious since the recent findings of plasmodia of rodents (P. berghei, P. vinckei, P. chabaudi), squirrels, mouse-deer, bats and antelopes transmitted by some Anopheles species in nature. There is also evidence that some mosquitos other than Anopheles may be infected with animal plasmodia. More exact techniques for distinguishing the sporogonic stages of human malaria parasites from others are needed. The fluorescent antibody technique introduced by Corradetti (1964) and also by others may be of practical value when it is simplified and adapted to field conditions.

5. Epidemiological importance of simian malaria

The present concept of the epidemiology of human malaria is based on the conviction that there is no animal reservoir of the infection and that as a rule malaria is transmitted within the human race.

Strictly speaking this concept ceased to be valid with the discovery of the parasites of higher apes experimentally transmissible to man through the Anopheles. Malaria of anthropoid apes is geographically limited to small areas of West Africa such as Sierra Leone, Liberia, South Cameroons and Lower Congo, where the three parasite species close to their human homologues were recorded. Nevertheless the rarity of the anthropoid apes, the distance between their natural dwellings and human habitations, and other ecological barriers between man and these animals make any outbreak of human malaria, introduced from this reservoir, most unlikely and for all practical purposes the animal reservoir of malaria of higher primates can still be ignored.

The situation is rather different with regard to malaria of lower monkeys and needs a careful assessment through intense ecological and parasitological studies. First of all, the lower monkeys exist in a far greater number of species than the apes and their total population is far larger. Their geographical distribution covers the areas of intense malaria such as central South America, tropical Africa and large areas of the Far East (India, Malaya, Philippines, Indonesia, etc.). The contacts between man and lower monkeys are generally much closer and it suffices to remember the hordes of semi-domestic rhesus monkeys in India to understand this point. The host preferences of Anopheles vectors for man and monkeys are often almost the same. Finally, the wide range of Anopheles species that are able to transmit experimentally some species of malaria parasites (at least seven Anopheles species can transmit P. cynomolgi to rhesus) is of considerable practical interest. Some of these species are sylvan Anopheles with exophilic habits and not likely to be affected by the use of residual insecticides.

Previously unsuspected human-animal disease relationships are being reported with increasing frequency. This can be explained by the constantly changing interactions between the host, the parasite and the environment, by greater facilities for biological study and by the improved means of communication bringing the research worker directly or indirectly closer to the hitherto little known areas of the world.

The study of the malaria zoonosis in some parts of the world is now of far greater importance than before. Such a study must consider the following points:

(1) Ecological study of the enterrelation between the simian host and its natural environment.

(2) Study of the host-parasite relationship in malaria infections of monkeys.

(3) Study of the dynamics of the infection of the human host with parasites of simian malaria.

(4) Geographical and focal distribution of malaria zoonosis in nature.

The approach to the investigation of malaria zoonosis should be synecological entailing the study of man, animals, the causative agent, its arthopod vector and the physical environment. Nevertheless the research on the natural history of the parasite should be our chief concern since the infecting organism is the pivot round which the investigation revolves.

Garnham points out that all infective human diseases must have been zoonoses at one time of the evolutionary period and that the present malaria parasites common to man and to anthropoid apes are survivals from that epoch and represent a primitive rank of the infective agent with a wide range of host specificity.

This discovery of a potent link of the human disease with the animal world is not new but it is interesting that some striking examples of such an extension of our knowledge have happened during the past ten years. This happened with regard to yellow fever and other viruses and also to two important tropical helminthiases. It was thought that the eradication loiasis would be easy through chemotherapy combined with anti-chrysops measures but Gordon and his colleagues in the Cameroons showed that monkeys are a reservoir of Loa-Loa and can maintain the chain of infection independently of man. Still more recently Edeson & Buckley in Malaya and Nelson & Heisch in East Africa showed that filariasis may be a zoonosis. In Malaya there is a reservoir in dogs, cats, pangolins and monkeys; in Africa probably in dogs and other animals.

In the present state of our knowledge and in spite of all the additional information collected during the past few years the conclusion of the Expert Committee on Malaria (1961) quoted on page 3 still stands unchallenged.

In the final conclusion it would be wrong to exaggerate the importance of the malaria zoonosis in the global programme of malaria eradication. The areas where foci of human malaria could perhaps be maintained from the animal reservoir of infection are few and relatively small in relation to the enormous territories where monkeys do not exist or are in very small numbers, or where the animal malaria parasites are absent or non-infective to man or not transmissible by those Anopheles which transmit human malaria.

The fact that malaria eradication has been an outstanding success in India, Ceylon and Taiwan where simian malaria is common indicates that the important discoveries of the recent years need not be interpreted as additional obstacles to malaria eradication in some parts of the world.

It is only in some parts of the world where foci or sporadic cases of malaria persist in spite of total coverage by residual insecticides and in spite of an efficient surveillance system that the possibility of a persistance of human malaria maintained through the ecological system monkey → $vector^A$ → man → $vector^B$ → man could be expected and appropriate action should be taken.

There are many ways of controlling the zoonoses and the seemingly simplest is to eliminate the wild animal reservoir; practical difficulties of such an undertaking are however considerable and other methods would have to be envisaged if they prove to be necessary. It should not be forgotten that the discovery of the transmission of simian malaria to man and vice versa is of great potential importance in chemotherapeutic research aiming at the development of better antimalarial drugs.

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