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Evolution of the Primate Malarias

THE evolution of the Haemosporidia has occupied the attention of many investigators and detailed discussions of the subject have been presented by Baker (1965), Ball (1943, 1960), Bray (1957, 1963), Bruce-Chwatt (1965), Christophers (1934), Garnham (1955, 1963, 1966), Manwell (1955), and others. The subject is extremely complex since not only must the evolution of the protozoan be accounted for but the concomitant evolutionary development of both the vertebrate and invertebrate hosts as well. Conclusive proof has not been presented to substantiate a particular evolutionary scheme for these parasites and their hosts and it seems unlikely that incontrovertible evidence to support any particular theory will be forthcoming. However, the subject does provide exciting grist for the evolutionary biologist to the extent that now it is more than an academic exercise. There are some very practical considerations to the evolutionary trends in the primate malarias and these will be discussed in more detail later.

Most workers agree that the malaria parasites descended from a coccidian ancestor. However, there are two schools of thought as to whether this ancestor was parasitic in an insect host or in the intestine of a vertebrate. The strongest evidence for the theory of an insect origin of the malaria parasites has been put forth by Huff (1938, 1945) and concentrates on two fundamental observations: 1) The parasites are found in a very diverse group of vertebrates (reptiles, birds, and mammals) but the invertebrate hosts are always dipterans. Development patterns in the insect are similar in all the species of malaria parasites and the invertebrate hosts form a much closer group than do the vertebrate hosts of the same parasites. 2) The Haemosporidia are relatively apathogenic for the insect in contrast to the situation in many of the vertebrate infections. Traditionally, high levels of pathogenicity in a host-parasite system are considered to be indicative of a recent association. There is undoubtedly an increased potential for survival in any parasite that creates as little discomfort as possible for its host and obviously there is no real lasting advantage to a parasite which destroys its host. Ultimately, this logic can be extended and symbiosis becomes the goal of all parasites. If this tenant is accepted, it is reasonable to assume that less pathogenic associations are older than those in which the whole gamut of the host's resistance mechanisms are forced into play. It is thus reasoned, by many workers, that the malaria parasite has been in association with the insect for a longer period than it has with the vertebrate host and, therefore, the coccidian ancestor of the Haemosporidia was originally an insect parasite.

The first of these two arguments is plausible and difficult to refute. Christophers (1934) suggested that the association between dipterans and plasmodia was established because of the tree dwelling habits of mosquitoes, birds, rats, and monkeys. This argument does not appear to be very strong and is based on the assumption that since the initial vertebrate infections were possibly in reptiles, these animals were tree dwellers also. Such an explanation does not help to understand the failure of the protozoans to develop in fleas, ticks, lice, and mites since certainly these ectoparasites intimately share an environment with their hosts which probably antedated the dipterans in the development of a blood-sucking activity. Thus Christopher's argument is an interesting one but seems much less convincing than the evidence presented by Huff to support the probable insect origin of the coccidian ancestor of the contemporary members of the

genus *Plasmodium*. (The same idea was put forth by Fantham (1936) but without elaboration).

It is interesting to note how a different emphasis can influence the interpretation of the same information. Huff considers the dipteran hosts of malaria parasites to be closely related when compared to the vertebrate hosts of the same parasites. At the same time, Bruce-Chwatt (1965) refers to the same group of insects as "diverse". Thus the same information has been used to support the insect origin of the malaria parasites (Huff) and the antithesis of this point of view (Bruce-Chwatt).

The second body of evidence is, in our view, somewhat less convincing. The absolute associations between pathogenicity and the age of a particular host-parasite system is possibly too simple. One cannot argue with the biological success of symbiosis over parasitism. However, we have to agree with Ball (1960) in that although long host-parasite associations frequently result in lowered pathogenicity there is no reason to assume that this is always the case. In addition, it should not be assumed that a new host-parasite association will be pathogenic. If we accept the proposition that the developmental sequence was from free living forms, to commensals, to parasites, then apathogenicity actually preceded pathogenicity.

Support of a coccidian parasite of the vertebrate intestine as the ancestor of the Plasmodiidae comes primarily from Manwell (1955), Bray (1957, 1963), Baker (1965), Bruce-Chwatt (1965), and Garnham (1966). Manwell (1955) notes that malaria parasites occur in birds and reptiles which probably preceded the blood sucking diptera in their evolution. Baker emphasizes the tendency of coccidians of the vertebrate intestine to become tissue parasites as further evidence to support the intestinal coccidian as the most likely ancestor of the malaria parasites. Garnham (1966) points out the difficulty in visualizing the existence of the plasmodia as dipteran parasites without intervention of a vertebrate if the life cycle in these insects was similar to that seen in contemporary species of *Plasmodium*. Bray presents a well constructed discussion of this subject in which he points out that the developmental stages of malaria parasites found in the vertebrate host seem to be reversed if the parasite ancestor had been an insect coccidian. In other words schizogony and gametogony should be in the mosquito host and sporogony in the vertebrate host.

The first of these arguments is interesting but the parasite could well have evolved after the blood sucking dipterans were on the scene. The second argument is important in that it reveals the potential of the coccidian intestinal parasites to invade tissues, but such a potential did not have to be realized.

The last two arguments of Bray and Garnham are possibly the most convincing in defense of a vertebrate coccidian as the ancestor of the malaria parasites in that they seem to offer the greatest challenge when one is searching for alternative explanations.

It is our conclusion that the immediate ancestor of the plasmodia is still not clear. However, the greatest weight of available evidence seems to support the position that a tissue invading parasite of the vertebrate intestine, in a reptile, found its way into the blood of the animal and eventually into a blood-sucking dipteran. The peculiar association of mammalian malarias and culicines probably reflects an early development of rather circumscribed feeding habits on the part of the mosquitoes. The perplexing absence of involvement in the life cycles of these parasites by other blood sucking arthropods, namely fleas, ticks, mites, and/or lice remains one of the most difficult aspects of this problem to understand if the parasites did arise in the vertebrate and therefore were presumably provided with many opportunities to adapt to some, if not all, of this latter group of the ectoparasites.

The long period between the initial efforts of the primitive tissue invading coccidian to adapt to the blood stream of a vertebrate and the digestive tract of a blood sucking dipteran, and the development of our contemporary genera and species of the malaria-like parasite remains obscure. Undoubtedly there were many failures as new vertebrate and invertebrate hosts were tried. However, these efforts were successful to a large degree since the genus *Plasmodium* alone is now found in all major groups of terrestrial

vertebrates and is represented by a large number of distinct species. As the malaria parasites evolved, they maintained certain basic features of morphology (particularly pigment production in the erythrocytic stages), life cycle (all presumably have schizogonic development in both fixed tissue cells and circulating blood cells of the vertebrate host) and host range (all undergo a sexual period of development with the subsequent production of sporozoites in the alimentary tract and haemocoele of a dipteran). To discuss the evolution of all the species of *Plasmodium* is beyond the scope of this work; so, we will direct our attention to a more detailed examination of those forms found in primates.

The differentiation of the primate malarias is relatively recent and the trends that produced the currently known aspects of speciation and distribution are, in our opinion, part of a dynamic process which is still not completed. Many theories have been advanced in an effort to correlate the distribution of contemporary primate plasmodia with various known aspects of their vertebrate hosts; i.e., physiology, distribution, and ecology. The evolutionary relationships of most parasites must necessarily be speculative since direct knowledge is confined to very recent history. This is particularly true of the malaria parasites since they were discovered less than 100 years ago. Prior to this century, we have only vague historical references to clinical entities which we struggle to attribute to currently known disease agents. Therefore, an understanding of the evolution and interrelationships of the contemporary species of primate plasmodia and associated aspects of host and geographic distribution will depend, for the most part, on our knowledge of primate evolution.

Different approaches to the evolution of primates vary in detail but there are some concepts on which there is considerable agreement. There seems little doubt that there was a lemuroid-tarsieroid ancestor for all of the contemporary primate species and that the evolutionary changes resulting in today's simians and anthropoids began in the middle or late Eocene some 35-40 million years ago. In addition, there is little conflict over the idea that the ancestor of the New World monkeys was isolated from the main Old World line at a very pivotal point when a variety of new morphological and physiological features were being tested for their ability to survive. Thus, the non-human primates of the Western Hemisphere are monkey-like, reflecting a close ancestral relationship to the African and Asian forms. However, differences between the two great groups are in many ways quite marked, revealing an extensive period of isolated development.

The Old World primate stock undoubtedly produced not only the common monkeys of Asia and Africa but all of the anthropoids as well. There is a considerable amount of controversy concerning the precise line through which man eventually evolved. Three major theories on the branching points between pongids and hominids were reviewed by Mayr (1963). Briefly, these three theories are: 1) that the hominid line branched from the common stem before the living anthropoids split into three different lines; 2) that the hominid line branched off after the gibbon line but before the pongids split into lines that eventually gave rise to *Pan* and *Pongo*; and 3) that the hominid line branched off from the line of the African apes at a comparatively recent date and long after the pongid line had split into an Asiatic (*Pongo*) and an African (*Pan* and *Homo*) branch. Fossil records supporting either of these theories are limited but hemoglobin and serum protein data make the third alternative more likely. Supportive evidence for the closeness of the hominid and African lines of evolution has been reviewed and expanded by Dunn (1966), with particular reference to their parasites.

Efforts to orient the evolution of the malaria parasite to the general trends of primate evolution have been successful only to a limited extent. It would be convenient to pick up the story with a primitive hepatocystis-plasmodium like ancestor in one of the lemuroid progenitors of contemporary primates and follow the development of both the parasite and the primates through successive evolutionary stages. Unfortunately, such an approach runs into difficulties when the current distribution of the primates and their plasmodia is considered.

There are true plasmodia in the lemurs of Madagascar but the biological isolation of this island presents many problems in evolutionary origins. Also, considerable difficulty is found in accounting for the distribution of malaria parasites among the living species of monkeys. The proliferation of species in Asia presents a probable picture of long association of a host-parasite system and indicates a considerable amount of success on the part of the parasite. If we confine our examination of parasite-primate evolution to southern Asia, then we encounter relatively little difficulty in arriving at a sequence of events which lead directly to current associations of monkeys, apes, and man and their respective malarias.

We can readily postulate a probable aperiodic hepatocystis-like parasite in a cercopithecoid ancestor of the Old World monkeys. After an ecological separation of Asian and African monkey groups, the parasite in the Asian monkeys began to undergo a series of changes which gradually produced malaria parasites with biological and morphological characteristics with which we are familiar today. It is probable that a quartan branch from this main line gave rise to contemporary tertian and quartan species in various primates as well as the successful but geographically limited quotidian experiment, *P. knowlesi*. Meanwhile, *Hepatocystis* resulted from a more conservative and less innovative series of changes from the primitive tissue coccidian than was involved in the evolution of the plasmodia. The stimuli responsible for the development of the malaria parasites were either not associated with African primates or, malaria-like parasites developed but were not initially successful. Thus, in Asia a reasonable hypothesis concerning the simultaneous development of primates and their malaria parasites can be proposed. However, since there are both primates and primate malarias in Africa and in the Western Hemisphere, any hypothesis concerning the origins must encompass these forms, too.

In Africa, the human and ape malaria parasites are remarkably similar and at least two species, *P. malariae* and *P. schwetzi*, may be shared. This situation fits well with the hypothesis that the hominid line was a comparatively recent offshoot from the African ape line if we assume that the malaria parasites were evolving at the same time and through the same lines as the primates. However, only one species of plasmodia (*P. gonderi*) has been identified in African monkeys although *Hepatocystis* is quite common in these animals. It is difficult to understand the evolutionary sequence that would yield six species of *Plasmodium* representing three basic types in the apes and man in Africa and in the process see the development of only one species of one type in monkeys in the same area. It is possible that ancestors of living African monkeys had malaria parasites at one time which have been lost subsequently. However, these factors seem to indicate that the malaria parasites in apes and man in this area were introduced relatively recently rather than the end product of a long evolutionary process involving both the host animals and their parasites.

Problems are also encountered in the Western Hemisphere when the primates and their malaria parasites are considered. The evolutionary line of the New World primates was isolated from the Old World line quite early. There are no hepatocystis-like parasites in New World monkeys. The success of the primates in the Western Hemisphere is well demonstrated by the large variety of genera and species of these animals found in Central and South America. The Haemosporidia have not been as prolific; there are only two species described from the many potential host animals. *Plasmodium simium* seems to be limited in both host and geographic distribution being found only in howler (*Alouatta* sp.) and woolly-spider (*Brachyteles arachnoides*) monkeys in the forests of southern Brazil (Deane *et al*, 1969). *Plasmodium brasilianum* has a much wider range, but there are large areas, with suitable host animals, where it is not found, and, where natural infections in the same genera of monkeys, vary considerably even over relatively short parts of its range. These factors would seem to indicate that these host-parasite associations are much more recent than the 35 million years since the apparent isolation of the primitive ancestral primates of the New World by continental drift. Finally, the two species of

plasmodia from this area are virtual duplicates of the human *P. vivax* and human and chimpanzee *P. malariae*, a phenomenon that severely challenges even the most extravagant views of convergent evolution. It is almost as though these parasites arose full grown like the mythological appearance of Athena from Zeus' head.

The evolution of the Haemosporidia has been reviewed by Baker (1965), Bruce-Chwatt (1965), and Garnham (1966) where efforts were made to correlate the evolution of the primates and their malaria parasites. Some of the problems associated with such an effort have been pointed out in the preceding paragraphs. We believe that the most uncomplicated and, therefore, possibly, the most likely explanation for the peculiar features of host and geographic distribution, as well as species proliferation of the primate malarias, has not been given a full hearing. Our suggestion is, that the nidus of the primate plasmodia universe lies somewhere in the jungles of Southeast or South Central Asia and that there, there has been a simultaneous development of non-human primates and their malaria parasites. Possibly during the early Pleistocene, some one to two million years ago, there appeared the first of many incursions into this reasonably stable millieu by a new and more highly evolved primate, from the west and north, in the form of an ancient hominid ancestor. This invader, the product of a long evolutionary sequence in Central Africa, was already demonstrating that peripatetic feature so characteristic of his descendants. The invader was still a hunter and forest dweller and, therefore, shared the forest environment, including anopheline mosquitoes, with the more primitive native primates of the area and their malaria parasites; the latter, probably already possessed characteristics of morphology and periodicity similar to those we recognize today. The situation was thus ideal for the introduction of the parasites into this *new* primate. Such a potential still exists, when man and non-human primates intimately share the same jungle environment.

The peripatetic nature of the *restless primate* increased and over the next 500,000 to one million years introduced, probably on numerous occasions, his malaria parasites into the apes and monkeys and his fellow hominids of West and Central Africa. It was in this African environment that the biological experimentation on the part of the parasites which eventually produced *Plasmodium schwetzi*, *P. ovale*, and the *P. falciparum-P. reichenowi* complex took place. It seems probable that the ancestors of *P. malariae* and possibly even *P. vivax* came out of Southeast Asia pretty much as we know them now. The older quartan parasite found an environment in which it could readily develop and thus the quartan malaria species of man and the African apes are considered generally to be conspecific.

The situation was less sympathetic for the tertian parasites. The indigenous negroid hominids in Africa were even then probably not very receptive to this latter group and adaptations were necessary. From the vivax-like stem developed a morphologically similar species, *P. ovale*, that was capable of surviving in the indigenous hominds. At the same time, a similar type of adaptation was taking place in the anthropoid cousins of the hominids in the area with the development of an additional species from the same stem, *P. schwetzi*. Coatney (1967) proposed that *P. schwetzi* was in all likelihood a chimpanzee equivalent of *P. ovale*. Such a relationship would not be surprising in the light of the hypothesis being presented here. However, it would be difficult, if not impossible, to say whether *P. ovale* and *P. schwetzi* arose simultaneously from the introduced *P. vivax* stem, or, whether the development was sequential in man and then the chimpanzees, or, the reverse. Probably the most interesting and most recent manifestation of attempts by the tertian parasite stem to adapt to African primates is seen in the development of the *P. falciparum-P. reichenowi* complex. Three features of *P. falciparum* seem to set it apart. First, the presence of crescent-shaped gametocytes; second, the tendency toward deep circulation schizogony; and third, the apparent absence of a mechanism, either relapse or long term recrudescence, by which the parasite can more safely assure its survival. It is interesting that each of these characteristics can be seen to a greater or lesser extent in parasites of

non-human primates in Asia. The potential of the Haemosporidia for producing crescent-shaped gametocytes has been well demonstrated by the bird parasites. In the primates, *P. coatneyi* and *P. fragile* are most closely related to *P. falciparum-P. reichenowi*. In the latter parasites, there is a definite tendency toward the production of oval gametocytes, especially in the younger stages (Fig. 27, Plate XLII). Deep circulation schizogony is present in *P. coatneyi* and *P. fragile* of Asian monkeys. The possession of a true relapse mechanism appears to be limited among the primate malarias. This phenomenon has been seen in *P. vivax*, *P. cynomolgi*, *P. ovale*, *P. fieldi*, and *P. simiovale*, all of which are tertian parasites in stippled cells. Relapse is not known to occur in *P. fragile* or in *P. coatneyi*, and is apparently absent in all the quartan species, including *P. malariae*. Thus *P. falciparum* and *P. reichenowi* are not far removed from the main stem of evolution in the primate malarias when we consider that there are other similar developments from the tertian ancestor among Asian non-human primates.

The dynamics of this relationship between the malaria parasites and the primates probably remained fluid for thousands of years. As the migratory habits of the hominid increased he carried his parasites to all areas of Asia, Africa, and Europe and, if anopheline mosquitoes were present, a focus of infection was established. Eventually, in the 16th century, man introduced his malaria parasites into the last remaining fertile area for their development. With the arrival of the southern European conquerors and their West African slaves into the Carribean area, the last large malaria free primate population, in an appropriate environment, had been drawn into a process that had begun millions of years previously in the monkeys of Southeast and/or South Central Asia. This latest experiment is, of course, still underway in the jungles of Central and South America. At the present time, the parasites have had unqualified success in human populations of the area, both indigenous and recently introduced. The situation in the non-human primates has been less successful but at least two of the human forms seem to have established themselves in the monkeys, in certain areas, of Central and South America. The older and, apparently, the more stable quartan *P. malariae* has become well adapted as *P. brasilianum* to a variety of monkeys in many parts of Central and South America. The tertian parasites have adapted less readily in the New World monkeys with only limited success as *P. simium* in the howler and wooly-spider monkeys of Brazil. The *P. falciparum* line has not, in so far as is presently known, found a suitable host among the nonhuman primates of the Western Hemisphere.

The hypothesis that primate malarias arrived in the New World with Europeans and their West African slaves in the 16th century is not new. Recent authors who have defended this point of view have included Boyd (1949), Jarcho (1964), and Dunn (1965). However, there is a considerable body of literature that supports the existence of human and other primate malarias in pre-Columbian America. Bruce-Chwatt (1965) has presented an extremely interesting and well written article on this subject in which he summarizes the three kinds of evidence which are used to support the extreme antiquity of malaria in America; i.e., linguistic, botanical, and historical.

The linguistic evidence seems to be primarily oriented around the appearance in the Indian dialects, from both Mexico and Peru, of words which were roughly translated to mean chills and fever. The earliest translations were made by Spanish soldiers and priests who were familiar with chills and fever (probably from malaria) and, therefore, their interpretation of Indian words referring to general classes of illness may not have been without bias. In addition, "chills and fever" is not a syndrome unique to malaria.

The botanical evidence is probably even more fraught with uncertainty than the linguistic evidence. The romanticism that has developed around the discovery of the effectiveness of an extract of cinchona bark against malaria has left us with a number of intriguing stories but little concrete evidence (see Haggis, 1941). Considerable importance is given to the belief that the use of cinchona was widespread among the New World Indians for the treatment of fevers. Since cinchona extract is known to be a

febrifuge there is no reason to assume that the fever being treated was malaria. Undoubtedly there were many febrile agents in the area. Finally, there is a growing body of evidence as reviewed by Jarcho (1964) that cinchona was not widely used in Indian medicine.

The historical evidence is, in our opinion, not only controversial as Bruce-Chwatt points out but, also, unconvincing. There is no doubt that the early Spanish explorers in the Caribbean and along the Atlantic coasts of Central and Northern South America suffered terribly from outbreaks of disease. However, the evidence for these early problems being due to malaria is vague in the extreme. The earliest slaves probably arrived in Cuba in the first decade of the 16th century. They undoubtedly brought malaria with them, but the Europeans themselves were also subject to malaria and undoubtedly assisted in establishing the parasites in the New World. Bruce-Chwatt (1965) notes that since the number of slaves was initially small, it is doubtful if large scale epidemics could have started with such a small source of parasites. There are two factors to be emphasized here; first, the evidence that the early disease outbreaks in the Spanish colonies were due to malaria is, to say the least, tenuous. Second, in the settlement areas, the Indians, as non-immunes, constituted an immediately available and readily infectable population. There is no doubt that human malaria became well established early in the Spanish conquest of Central and South America. Actually, this is not surprising considering the hardiness of the parasite and the fact that it was introduced into an area with a surfeit of both vertebrate and invertebrate hosts and an environment for transmission that has proved to be most efficient.

Possibly the most convincing evidence for the post-Columbian introduction of malaria into the New World is the difficulty in finding any other means by which it could have arrived. (We assume that there is no question that primate malarias were *introduced* into the New World. The alternative would be that these parasites evolved in the Western Hemisphere and became established only recently in the Old World primates; a proposal for which we believed there is little, if any, support.) The advocators for the existence of malaria in pre-Columbian America usually postulate that the parasites were introduced with man. Most anthropologists agree that man arrived in America via a land bridge from northeastern Asia between 15,000 and 25,000 (possibly as much as 40,000) years ago. More recent movements of small numbers of people from islands in the Central and Eastern Pacific to South America would also seem possible since the epic voyage of the Kon-Tiki. Finally, there is now no doubt that the Vikings reached the shores of North America 500 years before Columbus. Thus, there were at least three opportunities for man to have introduced malaria into the Western Hemisphere prior to the advent of the Conquistadores, with their malarious slaves, into the tropical area of the Caribbean.

What are the chances that any or all of the migrants were infected with malaria when they arrived? The land bridge from Asia connected two areas which have been, during historical times at least, incompatible with the transmission of malaria, and the evidence available indicates that the climate at the time of the migrations was at least as severe as today (Hopkins, 1959). Additionally, there is no evidence that there was any malaria-like illness among North American Indians prior to historical times.

Assuming that *Homo sapiens* did cross the Pacific to reach the shores of South America, it is probable that such a movement was made in stages using the islands of the Central and Eastern part of this area. These islands have been, and are now, free of anophelines and hence malaria in historical times, a biological condition that did not occur suddenly and therefore probably reaches back some distance into prehistory.

Finally, during the time the Vikings were journeying to Iceland, Greenland, and North America, their home area was free of malaria. Therefore, it would seem difficult, if not impossible, for malaria to have accompanied any of the pre-Columbian human invasions into the Western Hemisphere.

There are, undoubtedly, many flaws in the hypothesis we have presented. However, it does account for most of the known aspects of the

biology of the primate malarias especially with reference to morphology, host, and geographic distribution. The intimate relationships between the plasmodia of man and non-human primates is possibly as recent as one million years, and there were probably fairly consistent interchanges throughout the long history of man's development. Obviously, such an exchange was related not only to the biology of the parasites in question but to the specific ecological niches which were occupied by man and other primates. As man evolved from a hunter and forest dweller into a planter and builder of houses, he became more and more separated from the vectors of non-human primate plasmodia and the biology of the now more or less separate groups of parasites began to diverge. The trend toward the separation of the malaria parasites of man and non-human primates has probably been progressing for thousands of years. However, the potential for exchange remains. This was demonstrated by the arrival of malarious Europeans and Africans in the New World early in the 16th Century and, through intimate sharing of anophelines with native primates, malaria was introduced to them. Such exchanges still occur, as shown by two recent reports of natural infections in man with malaria parasites of monkeys. Chin, *et al* (1965) documented a human infection with *P. knowlesi* from West Malaysia and in the same year Deane *et al* reported a human infection with the vivax-like *P. simium* which was believed to have been contracted in a forest area outside São Paulo. In each of these situations, man had introduced himself into the forest environment where transmission of malaria among the nonhuman primates was constant.

When such exchanges of parasites occur today and man is on the receiving end, we have a zoonosis. The situation with regard to the monkey parasites of the New World can be described as an anthroponosis or a reverse zoonosis if the point of view is particularly anthropocentric. Thus, the study of the evolutionary history of the primate malarias becomes something more than an academic exercise, since such information may provide an insight into future trends in the relationships among these parasites and help to assess the zoonotic potential in human malaria. At the present time, the potential role of the simian and anthropoid malarias in human infections is still primarily a matter of speculation.

The genus *Plasmodium* has been very successful in monkeys, apes, and man in Asia since it infects naturally every genus of contemporary higher primate in the area. All of the primate malarias have their origin in Asia except *P. falciparum* and *P. ovale* which, according to the hypothesis presented here, probably originated in Africa. The tertian species are found in a variety of host animals which may be a reflection of the much less specific vector requirements in these parasites than in the quartan species, thereby providing more opportunities for their introduction into new hosts. *Plasmodium knowlesi* is the only quotidian malaria of primates. It has particular vector relationships which, combined with the lethal impact on monkeys other than the natural host, have served to keep it confined to the jungles of Malaysia, the Philippines, and, possibly, some islands in Indonesia.

In Africa, there has been a great reduction over that seen in Asia not only in the number of species present but in the host and geographic range in which they have been successful. It is proposed that all of these species developed from malariae-vivax stock introduced from Asia by a hominid ancestor. In Africa, the tertian parasites have had considerable success, while *P. malariae* is the only quartan species found and the quotidian stem was too fragile to survive in this new and apparently hostile environment.

In American primates, the trend toward a reduction in species is more pronounced. The success of the human forms in indigenous primates in the New World is limited to only two species. It may be, that in the near future, *P. brasilianum* and *P. simium* will be made conspecific with *P. malariae* and *P. vivax*, respectively. Such a situation presents the problem of how extensive a period of isolation in a new host animal, associated with what level of physiologic and/or morphologic changes, is required for a new species of parasite to be recognized. We support the position that the human *P. vivax* and *P. malariae* are the immediate and recent ancestors of *P. simium* and

P. brasilianum, but believe that these latter parasites are nevertheless valid species, at least for the present, in spite of the close morphologic similarities between the monkey and human forms. Therefore, it would seem that the only really startling innovation in the development of the primate plasmodia outside of Asia has been the rise of the falciparum-like parasites of Africa. The remainder of the species in both Africa and the New World are closely related to the stock Asian forms.

The evaluation of the role of simian and anthropoid malaria in human disease would not be complete without a word on possible *new* simian malarias. Recent successes in cultivating human malaria parasites in owl monkeys from South America and splenectomized gibbons from Asia have served to remind us again that *Homo sapiens* was a possible source of the simian and anthropoid parasites of Africa and the New World and, that the evolutionary processes that brought about this development are dynamic and contemporary. New species of simian malaria may still be adapting in the jungles of Africa or South America.

The current status of our knowledge makes it difficult, if not impossible, to relate the evolution of primate malarias to the earlier offshoots of the same ancestral line in reptiles, birds, rodents, bats, and a few ungulates. Rodent and bat plasmodia are found only in Africa. Two of the three ungulate species are African and one is Asian. No non-primate mammalian malarias are found in the New World. The most puzzling aspect of the primate plasmodia is the presence of two species in lemurs on the island of Madagascar. These are malaria parasites in a true but primitive African primate. Probably this enigma reflects the long period of biological isolation of Madagascar from the mainstreams of either Asian or African animal evolution. *Plasmodium girardi* and *P. lemuris* are poorly understood parasites which may be examples of convergent evolution arising from the same hepatocytis-like ancestor as the other plasmodia of which *P. foleyi* (also from the lemur and considered by Garnham (1966) to be more probably *Hepatocystis* than *Plasmodium*) is the more direct, contemporary descendant.

Undoubtedly, there are alternative explanations for the evolutionary processes which gave rise to the current distribution of the primates and their malaria parasites. The hypothesis proposed here seems logical in the light of our present knowledge, suggesting that the origin of at least the primate malarias was in Asia and that man in his wanderings has been responsible for the introduction of these parasites into African and New World primates. For thousands of years man and non-human primates occupied the same environment with what was probably a fairly free interchange of malaria parasites. However, man's development as an agricultural animal tended to separate him ecologically from his simian and anthropoid relatives and at the same time from their malarial parasites. This trend has continued until it is obvious that today the relationships between the human and non-human primate malarias are very tenuous and, in the overall aspects of human health, of limited importance. However, it is probable that occasional cases of human malaria of simian origin will be detected in deep jungle areas of Asia, Africa, and South America once malaria eradication has advanced to a point where such cases can be individually evaluated.

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