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Paleogenesis and Paleo-Epidemiology of Primate Malaria *

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The Haemosporidia, which comprise the malaria parasites, have probably evolved from Coccidia of the intestinal epithelium of the vertebrate host by adaptation first to some tissues of the internal organs and then to life in the circulating cells of the blood.

The present opinion is that, among the malaria parasites of primates, the genus Hepatocystis *and the "quartan group" of plasmodia are the most ancestral, followed by the "tertian group"; from the evolutionary viewpoint the subgenus* Laverania *is probably the most recent.*

Studies recently completed and research in hand on malaria parasites of apes and monkeys, combined with the possibility of assessing the infectivity of new simian parasites to Anopheles *and to man, will be of great importance for a better understanding of the probable evolution of primate malarias. The fact that several genera of the Anthropoidea evolved in an ecological area where the association with the existing insect vectors of various plasmodia was close is suggestive of Africa as the original home of primate malaria. It is probable that the disease spread up the Nile valley to the Mediterranean shores and Mesopotamia, to the Indian peninsula and to China. From these main centres malaria invaded a large part of the globe.*

It is also probable (though not proved) that malaria existed in the Americas before the Spanish conquest, and there is some likelihood that sea-going peoples brought it to the New World long before Columbus's voyages. Modern immunological methods applied to the study of the mummified remains of ancient inhabitants of America may help to solve this question.

> "Des espèces, des races se sont éteintes, d'autres ont évolué. Et, si nous ne pouvons faire la preuve de l'existence de maladies anciennes, aujourd'hui disparues, du moins restons-nous rêveurs devant la continuité de certaines affections dont le temps, les milieux, le passage sur les êtres les plus divers n'ont pu modifier les caractères. Des millions d'années s'écoulent, des êtres disparaissent, d'autres surgissent; mais, toujours, la maladie est là pour les marquer de ses stigmates.
>
> "Dans la vie de notre planète, elle a joué certainement un rôle considérable, aussi bien dans l'apparition des moyens de défense que dans l'évolution des êtres."
>
> PALES (1930)

The study of origins of disease is once again attracting some attention. Among the many reasons for the awakening interest in the prehistory of malaria, three may have the greatest weight: recent discoveries about the evolution of man, the explosion of new knowledge about malaria of our simian ancestors, and the development of marvellously precise biochemical and immunological methods that offer much promise for future research.

PALEOGENESIS OF "MALARIA PARASITES"

Much has been written about the evolutionary approach to the study of infections caused by protozoa commonly and loosely referred to as "malaria parasites", as defined by Garnham (1963b).

From the early period of work on Haemosporidia, some parasitologists, and Mečnikov (1887) among the first, were struck by the similarity of their

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cycle of development to that of certain intestinal parasites of the order Coccidiida.[1] Pfeiffer (1892), Mesnil (1899), Schaudinn (1899) and Reichenow (1912) are quoted in this respect by Wenyon (1926), by Missiroli (1934) and by Manwell (1955), who state that Haemosporidia evolved from Coccidia which had adapted themselves to life in the blood and in the process of this adaptation acquired a second host. In both types of parasite, the infection of the vertebrate starts with the entry of the sporozoite into the cell; the subsequent schizont produces merozoites and these again become schizonts producing more merozoites. During the sexual development, the fusion of male and female gametes results in the formation of an oocyst and division into sporozoites which recommence the asexual cycle.

Although the differences between the Coccidia and Haemosporidia are many and considerable,[2] it is generally agreed that their common evolutionary history started with an ancestral, free-living protozoon which invaded the intestinal tract and maintained a simple life-cycle without an alternation of generations by multiplying within the same host and forming cysts discharged with the faeces. The next evolutionary steps comprised (as in *Eimeria* and *Isospora*) an invasion of the epithelial cells of the gut, with a life-cycle consisting of several asexual generations followed by a sexual generation and formation of an oocyst which is discharged and serves to infect a new host when swallowed.

In the Lankesterellidae of amphibia and reptiles, there is a gradual adaptation of an intestinal coccidium to the blood habitat (Adler, 1933); the schizogony and sporogony take place either in the intestinal wall or in the endothelial cells of the blood vessels, but the sporozoites penetrate the free cells of the blood and can be transmitted by a blood-sucking non-winged arthropod or by a leech. A parallel or previous evolutionary step can be traced in the invasion of the liver, through the portal system, to establish the developmental cycle in the bile duct epithelium (e.g., *Eimeria stiedae*) or in the endothelial cells of the capillaries of this organ (e.g., *Haemoproteus*) or in the liver cells themselves (*Hepatocystis*, *Plasmodium*).

Manwell's hypothesis (1955) that the plasmodia developed from Coccidia *via* haemogregarines has been vigorously developed by Bray (1957, 1963b), who maintains that in the subclass Coccidiomorpha the orders Coccidiida, Adeleida and Haemosporidiida should be given equal taxononomic status, the last of the three orders having derived from the first *via* the second.

The fundamental consideration is that of phylogeny, since Bray (1957) postulates that the ancestors of the Plasmodidae were haemogregarine-like parasites, whose first appearance in the blood-stream would facilitate transmission by blood-sucking arthropods.

Tracing lines of development in the Haemosporidia, Bray (1957) believes that the older line typified by *Haemoproteus* gave rise to the malaria parasites of amphibia, reptiles and birds while the more recent line typified by *Hepatocystis* represents the evolutionary stem of malaria parasites of mammals. This is in agreement with the trend of evolutionary change in the parasites since the original separation of birds and reptiles from the main evolutionary stem. Reptilian and avian species of malaria parasites are more numerous, have a wider geographical distribution and are better adapted to their hosts (Cameron, 1950) if one admits low pathogenicity as a criterion of adaptation.

In the light of the present knowledge the most primitive known parasite of the avian and saurian line is *Plasmodium* (*Haemamoeba*) *mexicanum*. In the case of mammals the most primitive is the " quartan group " of parasites, followed by the " benign tertian group " and by *Plasmodium knowlesi* with its *Hepatocystis*-like dependence on the liver; the subgenus *Laverania* (*P. falciparum* and *P. reichenowi*), the least dependent on the development in the liver, is probably the most recent. For malaria parasites of man this hierarchy was suggested by Knowles & Senior-White (1930).

Too little is known about malaria parasites of other animals to attempt any explanation of their evolutionary relationship. One step in the evolutionary history of Haemosporidia was of paramount importance—namely, the time when the blood-adapted parasites acquired the insect as their invertebrate host.

No better example of a " deployment " in Huxley's (1953) sense could be found: an original single group

[1] " Judging by what has been learnt about the micro-organisms of malaria one should regard them as belonging to a group of Coccidia, some representatives of which live within the cells of various animals . . . The micro-organisms of malaria differ from Coccidia since the former have no envelope or capsule which protects their ameboid body during the developmental stages " (Mečnikov, 1887; trans.)

[2] In the first the fertilization process and encystment of the zygote takes place in the vertebrate host, while in the second this takes place in the blood-sucking invertebrate, which shelters the oocyst in its body until it produces sporozoites.

became more numerous and more diversified and in doing so spread over the environment using the evolutionary opportunities available and enabling it to exploit the new environment more extensively.

Study of the paleogenesis of malaria may be the best example of Fischer's reference to natural selection as a " mechanism for generating a high degree of improbability ", and the longer the selection acts, the more improbable the results.

It is admitted that the close dependence of a group of parasites on a group of hosts indicates a degree of phylogenetic specificity which testifies to a long evolutionary relationship. Our existing insect fauna is only a small fragment of the aggregation of insects that occupied the earth during the past 250 million years (Zeuner, 1950; Carpenter, 1953).

Diptera evolved probably during the age of reptiles in the Permian but the first known fossil representatives of two-winged insects date from the Jurassic period about 150 million years ago, after the flowering plants appeared. Paleontological records of fossil Culicidae, summarized by Edwards (1923), Martini (1930), Bates (1949) and more recently by Christophers (1960), indicate that they existed in the Eocene (60-40 million years ago) but particularly in the Oligocene (40-30 million years ago) and may have differentiated much earlier.

The ancestral *Anopheles* stock became isolated during the intercontinental dispersion into several complexes which were then broken up into a number of genetically distinct species—a performance that, for each of them, may take about 500 000 years according to Zeuner (1950).

No fossil *Anopheles* have been discovered but the total number of mosquito fossils is still very small. Perhaps the new remarkable insect fossil finds in Rusinga and Mfangano in East Africa will show the presence of this group.

The study of distribution of mosquito species gives no clue for the explanation of the evolution of malaria, as mosquitos do not form a good basis for research in faunal geography. The figure of 1400 world species of mosquitos (Bates, 1949) rose by 1959 to 2426 valid species listed by Stone, Knight & Starcke (1959) and the highest number are in the Neotropical, Oriental and Ethiopian zoogeographical regions. Out of 312 species of the genus *Anopheles* given in a recent synoptic catalogue (Stone, Knight & Starcke, 1959) and reclassified by Reid & Knight (1961) only about 65 can be considered as vectors of four species of human malaria (Russell et al., 1963).

The fact that, as far as we know, malaria parasites of primates develop only in anopheline mosquitos leads to the assumption of a long evolutionary association and suggests that from an early stage anophelines adapted themselves to feeding on mammals and culicines on birds (Mattingly, 1960, 1965). Naturally, the insect-vertebrate life-cycle of the malaria parasite could not have evolved before the mosquitos developed their blood-sucking habits. If the original home of malaria was in the Ethiopian region it is certain that the *Anopheles* existed there well before the first hominids and the same is also true for the temperate climates where the penetration of man was preceded by that of the insect vector (Ross, 1964).

Obviously the chance of an *Anopheles* becoming a malaria vector depends on its inherent susceptibility to infection by a parasite species, but not less important are the biting habits, food preferences and life expectancy of the relevant mosquito. The fact that originally all malaria vectors must have been exophilic was stressed by Alvarado & Farid (1963).

It is certainly relevant that the anopheline fauna of the Ethiopian zoogeographical region is distinct and homogeneous. It represents a remnant of ancient forms and the primitive subgenus *Anopheles* occurs, though in a small number of species. On the other hand, the next oldest subgenera—*Myzomyia* and *Neomyzomyia*, the best vectors of malaria—are exceptionally well represented (de Meillon, 1947).

THE ORIGINAL HOST OF MALARIA PARASITES

For the past 25 years there has been much speculation on the problem whether the ancestors of malaria parasites originated in the vertebrate or invertebrate host. Huff (1938, 1945) was in favour of the view that plasmodia must have been parasites of insects and became secondarily adapted to their vertebrate host.

This argument is based on Theobald Smith's (1934) postulate that " the ancestry of the malaria parasite belongs to the insect because the most important, viz., sporogonic phase takes place in it " and on that of Mayr (1957) who said that " the long evolutionary association is shown when the development of the parasite is so closely correlated with the host as if it were one of its organs ". This concept has been considered by Garnham (1955), who stressed the higher degree of adaptation of Haemosporidiidea to the insect as evidenced by the apparent absence of pathogenicity to the invertebrate host.

It has been generally agreed that high pathogenicity indicates a newly established parasitism (Baer, 1951) since evolutionary selection would act against the more pathogenic strains of the parasite species as well as on the less resistant hosts. However, Caullery (1952) warned that parasitism may arise from an intermediate condition like commensalism, and Ball (1943) pointed out that pathogenicity can occur in old-established as well as in new parasites and stressed that all evolutionary theories based on this evidence alone are extremely precarious, especially in Sporozoa (Ball, 1960). Even if Huff's (1945) view may be tenable for haemoflagellates (Hoare, 1948), it is doubtful if it could be accepted in plasmodial infection. Manwell (1955), while refusing to commit himself, emphasized that Coccidia are typically parasites of vertebrates and those found in invertebrates do not have an insect host. Bray (1963b) believes that adaptation to a host is not related to geological time but to the number of generations upon which the selection acts, and is in favour of the origin of plasmodia in the vertebrate.

Adler (personal communication) stresses that *P. (Laverania) reichenowi* is not infective to man while *P. brasilianum* is, and yet phylogenetically the first is much closer to human plasmodia than the latter. The same argument could be used with regard to *P. malariae*, which is certainly an older parasite than *Laverania* and yet infects the chimpanzee more easily than *P. (L.) reichenowi* does. It is obvious, therefore, that pathogenicity is often so unpredictably related to the strain of a species (or a host) that one would hesitate to use this criterion.

Another fact in favour of the origin of malaria parasites from an intestinal *Eimeria*-like parasite of vertebrates prior to its adaptation to the insect vector is the fact that Haemoproteidae are transmitted by insects as diverse as Culicidae, Culicoides, Hippoboscidae and possibly Nycteribidae. It is unlikely that closely related organisms would have developed independently in such diverse genera of insects. On the other hand, plasmodia, having adapted themselves at some remote period to a particular mammalian stem, remain restricted to it through its association with *Anopheles* (Adler—personal communication).

Long-term association between the parasite and the host requires the establishment of a balanced condition which involves a series of adaptations related to the chance of infection, the virulence of the parasite and the resistance of the host. The interdependence between the parasite and its environment within the host has a selective value for the parasite and influences its speciation (Sandosham, 1960).

SPECIATION OF PLASMODIA

The problem of speciation in plasmodia has been recently discussed by Corradetti (1963), who pointed out that a parasite with a relatively low degree of specificity, able to survive in a host showing a marginal susceptibility to infection, may develop into a new race, which constitutes a potentially prespecific phase and needs only a sufficiently long isolation to become a species.

Thus, while a range of distribution of a given species of *Plasmodium* depends on the geographical distribution of the vector and on its bionomics, the evolutionary potential of the parasite is related to the range of specificity to the vertebrate host which offers conditions favourable to the accumulation of genetic differences through mutation and selection.

Alternation of phases in the life-cycles which has probably occurred during the evolution of malaria parasites must have had a selective advantage, since the presence of a suitable invertebrate host tends to increase the spread of the parasite. Huff (1958) points out that the alternation of vertebrate and invertebrate hosts in the transmission of malaria may be an effective screen for quickly discarding mutants that are detrimental to the species of *Plasmodium*.

The strict specificity of rodent plasmodia (e.g., *P. berghei*) gives them less chances for wider speciation through creation of new races. On the other hand, many avian plasmodia (e.g., *P. (H.) praecox*, *P. cathemerium* and others) have a considerable range of susceptible vertebrate and invertebrate hosts and are probably in the process of increased speciation. Plasmodia of primates are halfway between these two extremes; some have a narrow (e.g., *Laverania*), others a wider (e.g., *P. malariae*), specificity within the related vertebrate host and the invertebrate vector.

Since many parasitic genera are to be found in widely separated hosts, obviously the evolution of parasites does not always keep pace with the evolution of the hosts.

Noble & Noble (1964) gave the following explanation of the mechanism by which parasites evolve more slowly than do their hosts. Some members of a given species of host survive more easily than others when the environment changes. Those more fortunate hosts were slightly different from those

that were less suited (=adapted) to the new environment, but both groups of hosts possessed the same parasites. During the slowly changing environment all the hosts gradually changed, but many of these changes involved external features, and the internal parasites were not subjected to the same degree or type of environmental influences. The parasite's environment, however, did eventually change, but the lag in time between the change of the host environment and of the parasite environment resulted in a difference in rate of evolution. Thus, the parasite evolved more slowly than did its host. The relationship of the parasite to the external environment through the organism of the host and the importance of these ecophysiological conditions for the evolution of the parasite have been discussed by Moškovskij (1948) in his concept of functional parasitology.

The importance of the broad ecological approach to the study of human protozoal infections shared between man and other animals is obvious. The way to the better understanding of the natural history of arthropod-borne disease has been traced by Pavlovskij (1946-48), Moškovskij (1954), Beklemišev (1956) and summarized recently by Hoare (1962). The relationship between man and insects within an ecosystem and the role of human civilization in the dispersal of disease vectors have been described by Elton (1958) and by Bates (1962).

The problem of speciation is obviously related to the influences of the hosts, both vertebrate and invertebrate, upon the malaria parasites. An excellent review of this subject by Huff (1958) referred mainly to avian malaria, but experimental work on adaptive changes shown by malaria parasites of mammals is still in its early stage. The results of previous attempts at infecting man with malaria parasites of higher apes and *vice versa* (Garnham, 1954, 1955) did not indicate the possibility of human infections with *P. cynomolgi* or *P. brasilianum*—two findings that surprised us all.

Further work by Coatney and his colleagues (Contacos & Coatney, 1963) indicated that there is no evidence of gradual adaptation of *P. cynomolgi* to man following serial passages and that the " better " infections in man are related to the immune response of the host. Taking this into account, it is probable that successful experimental infections of man with many more simian malaria parasites will be reported in the not too distant future.

Recently Adler and his colleagues (Adler & Foner, 1961) succeeded in adapting *P. vinckei* to hamsters so that it lost its virulence to mice; interesting results were also obtained by Weiss & de Giusti (1964) following passage of *P. berghei* through tissue culture.

Many variables influence the development of protozoa in their arthropod hosts and their evolutionary importance is obvious. Garnham (1964) in his recent review stressed the lack of any precise knowledge of this subject, particularly with regard to the transmission of plasmodia by anopheline mosquitos.

It is increasingly clear that in any given region there are usually only a few species of *Anopheles* that are responsible for the transmission of malaria. The factors governing the vectorial capacity of a species belong to two groups—one ecological, the other physiological. This division is arbitrary but useful. The ecological factors include the degree of association with a vertebrate host; the physiological factors depend on the characteristics of the parasite, of the given *Anopheles* species and on the internal environment of the host. Although among the four common species of human plasmodia no sharp differences of vector susceptibility have been observed, it seems that geographical strains of a given *Plasmodium* may show just as much difference in infectivity as there is between various species of plasmodia. We do not know what factor influences this and must agree with Garnham (1957) that some inherent, probably enzymatic factor interrupts the plasmodial infection in non-susceptible mosquitos at any of the four stages of the sporogony.

That the susceptibility to infection may be a genetic characteristic of a given strain of mosquitos has been known since Huff's work (1938) with culicine vectors of bird malaria. Subsequent work with *Anopheles* was less clear-cut or negative, but the recent study by Ward (1963) on *Aedes aegypti* as vector of *P. gallinaceum* showed the proper methodology of such studies and the significance of such findings. Whether in some circumstances the simultaneous presence in *Anopheles* of a virus may interfere with the course of a plasmodial infection is still a moot point.

In the final account pathogenicity of the parasite or the capacity to invade the host-organism and to establish itself depends on its biochemical make-up. The basic metabolic processes of protozoa are common to any cell and this pattern must have evolved even before the appearance of free-living ancestors of protozoa. However, many aspects of the metabolic chemistry of parasitic protozoa have undergone profound adaptive changes. Although we are

beginning to know better the nature and the degree of the biochemical demands of malaria parasites, we cannot explain the nature of infectiousness. Moulder (1962) has excellently summarized our knowledge of the carbohydrate, protein, nucleic acid and lipid metabolic pathways and of the nutritional requirements of malaria parasites and outlined the defects of their biosynthetic set-up which makes their intracellular existence obligatory.

There has been a great deal of speculation about the evolution of parasites and parasitism. As mentioned before, it is impossible to generalize on one of the two main alternatives—whether commensalism precedes parasitism or *vice versa*. Parasitism may arise in different ways in different groups of animals: in some it may be preceded by a certain type of association; in others it may start by an unprecedented contact with the host. In both situations the ecological factors in the origin of parasitism are of paramount importance since the more frequently they meet the greater the opportunity for closer association. On this depends much of the specificity of parasites with regard to their hosts. Naturally other factors such as physiological and nutritional needs of the parasite throughout its life-cycle and the response of the host are not less important but they are the logical consequence of the first phase (Rogers, 1962).

The phenomenon of host-parasite adaptation has been recently approached from the immunological angle by Sprent (1962), following the lead given by Burnet's clonal selection theory. According to this approach the perpetuation of host-parasite association over evolutionary time involves the mutual " adaptation tolerance " so that the modification of the antigenic structure of the parasite goes *pari passu* with the correspondingly modified immunological response of the host, both factors operating through natural selection.

The value of Burnet's theory and its comprehensiveness can be best judged by the fact that it allows a Darwinian approach to the mechanism of immunity (Burnet, 1964). According to this, the antibody specificity related to the nature of the lymphoid system is genetically determined; all antibody patterns arise through a process of random emergence similar to somatic mutation and are afterwards subject to continuing selection for survival within the lymphoid cell population of the body. In such a process of cell-selection clones play the part of the species and subspecies in classical evolution.

RELATIONSHIP BETWEEN SIMIAN AND HUMAN MALARIA

Over thirty years ago Hegner (1928) and Christophers (1934), considering human malaria from a zoological point of view, wondered about the phylogenetic links between simian malaria and human infections. Our knowledge regarding plasmodial parasites of monkeys has greatly increased during the past five years, mainly thanks to the inspired work of the late Don Eyles and his colleagues in Malaya (Eyles, 1963).

The number of known plasmodial infections of apes and monkeys is today over 20, and it is likely that it will go on increasing as a result of recent work in Ceylon, India, South-East Asia, Brazil and Taiwan. A large unexplored territory for research on primate malaria is in Madagascar, Equatorial Africa, Indonesia, Central and South America and the Philippines.

A recent review by Bray (1963a, 1963c) and a symposium on simian malaria (*J. Parasit.*, 1963) summarized our present knowledge on this subject and Coatney's (1963a, 1963b) comments stressed the fact that at least in South-East Asia, where most of the present work has been done, the distribution of simian malaria and of some of its natural anopheline vectors creates a possibility of human infection with plasmodia of monkeys. Whether a natural monkey-man-monkey cycle of this anthropozoonosis can take place in nature frequently enough and on a scale that would maintain the animal reservoir of infection remains to be seen.

A distinction should be made between the man-animal interchange of parasites of anthropoid apes and that of parasites of lower monkeys. In the first case only *P. malariae* could be considered, though the likelihood is slim, and even then, as Bray (1960) remarks, it would be a greater threat to the chimpanzee than to man. In the second case the system involving the simian species and man with vectors feeding on both of them has yet to be demonstrated outside Malaysia (Mattingly, 1965).

A distinctive feature of simian malaria as known today is its focal distribution, the susceptible animals and the particularly effective vectors filling a well-defined ecological niche. In some conditions, when a focus of simian malaria is in the transitional zone, such as a forest edge, there is some likelihood of an interchange between human and simian malaria parasites. It is most unlikely that such a focus would create an obstacle to malaria eradication

in any substantial area, since conditions where human groups and lower monkeys live close enough for a free exchange of plasmodia must be very uncommon.

The examples of Ceylon and Taiwan, where the presence of simian malaria has not interfered in the least with malaria eradication, should be remembered as an argument against some too imaginative and premature conclusions.

There is little doubt that we are now only at the beginning of a new chapter in the study of plasmodioses and that intensive research on the infectivity of all plasmodia of primates to several species and races of Hominoidea including man would fill in the existing gaps in our knowledge.

The speed of research in this field will be recognized if it is pointed out that before 1960 no natural vectors of any species of simian malaria were known. During the past four years it has been found that, out of the 65 species of *Anopheles* recognized as vectors of human malaria, not less than 21 were natural or experimental vectors of simian malaria (Warren & Wharton, 1963; Bray & Garnham, 1964).

For the student of evolutionary aspects of simian malaria Garnham (1963a) outlined a fascinating perspective based on Huxley's 1863 hypothesis of the existence of an undifferentiated primate ancestor from which a series of successively more advanced forms branched off during the 70 million years that separate us from the Paleocene (see Fig. 2 below).

The assumption is that in the Tertiary, when first the Lemuroidea and then the New World superfamily of Ceboidea separated from the main stem, the genus *Hepatocystis* and later the ancestral "quartan group" of parasites (*P. inui*, *P. shortti*, *P. hylobati*, *P. brasilianum*, *P. malariae*) evolved and associated with the primates.

About 30 million years later, in the Oligocene, the Old World monkeys of the superfamily Cercopithecoidea acquired in the course of their evolution the "*ovale* group" (*P. fieldi*, *P. ovale*), the "*gonderi* group" (*P. gonderi*, *P. coatneyi*) and the large "benign tertian group" (*P. cynomolgi*, *P. cyclopis*, *P. pitheci*, *P. youngi*, *P. schwetzi*) possibly in this order followed by the quotidian *P. knowlesi*. During the Pleistocene, about two million years ago, characterized by the evolution of Pongidae and Hominidae, the most recent plasmodial subgenus *Laverania* evolved and became a parasite of man and higher apes.

As pointed out by Garnham (1963a), speculations on the evolution of malaria parasites are prone to fallacies and this fascinating theory must be regarded as tentative.

The evolutionary relationship between malaria parasites of man and those of higher apes in Africa has been discussed by Bray (1960), who pointed out the gradation of cross-infections, ranging from insusceptibility with *Laverania* to complete susceptibility with *P. malariae*. The probability that these parasites must have been shared by some previous common ancestor of higher primates is about the only conclusion that has some value. The assumed venerability of *P. malariae* in comparison with the relatively recent origin of *Laverania* may be arguable since the first remained as a single species while the second has separated into two. Perhaps the time alone is a less important factor in evolution than the biotic potential of the parasite.

The paucity of species of malaria parasites in the monkeys of Africa generally and, in particular, the absence of any quartan-like monkey malaria parasite constitute a serious gap in our speculations.

The assumption that the phylogenetically oldest parasites are chronologically related to the New World group of the suborder Anthropoidea may have to be revised in the light of the critical reappraisal of the evolution of tertiary primates by Simons (1963).

The Paleocene and Eocene primates found in North America are prosimian and their fossil record seems to end abruptly in the early Oligocene. In South America nothing whatever is known of primates before the latest Oligocene so that no overlap occurs between the primates of the two continents of the New World before the Pleistocene. It is probable that Anthropoidea originally differentiated in Africa from prosimians which may have reached that continent as far back as the Paleocene. Moreover, the Ceboidea might have originated from a different group of Prosimia than that from which the Old World monkeys came, because the similarities between the former and the latter are more apparent than real and the possibility of the independent development of a second primate stock may be considered (Büttner-Janusch, 1963; Harrison et al., 1964).

The first known records of large apes were found in the Miocene deposits in Europe, India and Africa and it is probable that *Proconsul* is close to the ancestors of the first hominids. The earliest remains of New World monkeys from the Miocene closely resemble the present genera and it is probable that the separation of this group was well advanced

10 million years ago (Harrison et al., 1964). It now appears that a new treasure-house of mammalian Miocene remains has been discovered in Uganda and it is likely that the present gap between the Miocene apes and the Australopithecines of the Pleistocene may soon be filled (Cole, 1964).

How the New World Anthropoidea acquired their plasmodia is a moot point. It is not impossible that they inherited them from their prosimian ancestors and that the evolution then proceeded independently from that of the Old World, but such parallelism would tax the imagination. Perhaps some plasmodial infections of New World monkeys are more recent, having originated from the early man when he invaded the American continent coming by sea from the East. The fact that man can be easily infected by *P. brasilianum* and the apparent absence of *Hepatocystis* in the New World are of interest in this respect.

The question whether man acquired his plasmodia direct from the higher apes or whether they have developed in the two families of Pongidae and Hominidae from malaria parasites of lower monkeys cannot be answered today, and Garnham (1963a) corrected some errors made by Livingstone's (1961) attempt to construct a workable hypothesis. The problem touches on the present controversy concerning the type of evolutionary progenitor of Hominidae, and the arguments for its being an arboreal brachiating ape are not more and not less acceptable than those favouring a social terrestrial primate such as a baboon or macaque (Büttner-Janusch, 1963).

AFRICA—AN EVOLUTIONARY CENTRE OF HUMAN MALARIA

Any extrapolation of the recent advances in our knowledge of simian malaria with regard to its relationship to human disease is bound to be premature. Nevertheless many conclusions of the primatologists agree with the postulated ancient association of malaria parasites with the ancestors of man, and the recent work on simian malaria confirms the close biological relationship within the living representatives of the suborder Anthropoidea and may help to trace the cradle of malaria as a disease of the human species.

The prosimian primates of the Eocene and early Oligocene (covering the span of 60 to 30 million years ago) gave rise to a variety of ape-like animals that in the Miocene (up to 20 million years ago) found in Africa exceptionally good climatic conditions for evolution and spread towards Asia as the continents were then united (Napier, 1964).

It was the Pleistocene period, at least one million years long and characterized by its succession of climatic changes and variation in the distribution of land and water that saw the main stages of the later prehistory of primates.

The rise and fall of sea-levels formed and disrupted the land bridges across which the early ancestors of man moved over their limited world. The evidence of the past thirty years shows that east and south Africa was the main evolutionary area of the primates. The four pluvial periods corresponding roughly to the glaciations of the northern hemisphere caused profound changes in the geography of that continent and in the major distribution of plants and animals over its surface (Fig. 1).

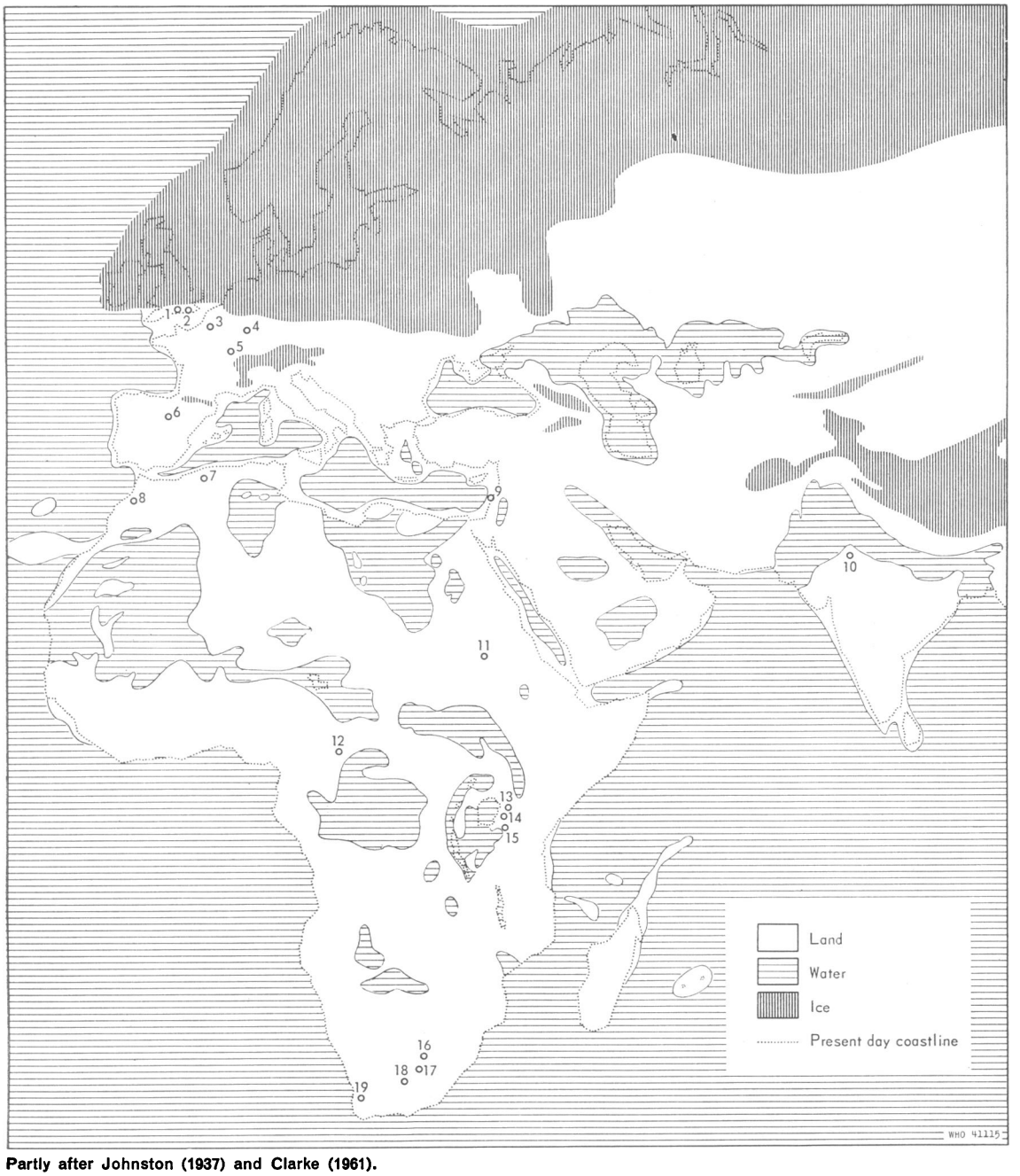
While there was relatively little difference in the coastline itself, the wetter climate created vast lakes and river valleys. A series of recent discoveries has confirmed the hypothesis that this was the part of the world where the superfamily Hominoidea first diverged into ancestral apes (Pongidae) and the family Hominidae, which then evolved into *Australopithecus*, *Pithecanthropus* and *Homo* (Harrison et al., 1964).

The emergence and dispersal of man is a subject that bristles with controversy and every new discovery changes the present picture. A great deal of evidence shows that the genus *Australopithecus* (including *Zinjanthropus* and *Paranthropus*), as defined by Le Gros Clark (1959), lived in Africa about one million years ago and was a hominid, though not necessarily the direct ancestor of man. *Pithecanthropus*—the other fossil hominid, found in Africa, Java, China and elsewhere—may be considered an intermediate between *Australopithecus* and *Homo*. Although its earliest remains date back to 600 000-700 000 years, it had a wide distribution and its relationship with *Australopithecus* remains close, and some species of these two genera must have been contemporaneous. The taxonomic position of the "early man" group given recently the highly controversial name of *Homo habilis* by Leakey et al. (1963, 1964) remains *sub judice*, but most authorities agree that all forms of *Homo* derived from a pithecanthropoid ancestor in the relative isolation and warmth of the African continent (Fig. 2).

Man's slow progress after the abandonment of his primitive habitat—through bipedalism, development and use of fore-limbs, tool-using and tool-making,

FIG. 1

PROBABLE OUTLINE OF PART OF EURASIA AND AFRICA DURING THE FOURTH GLACIAL PERIOD [a, b]



Partly after Johnston (1937) and Clarke (1961).

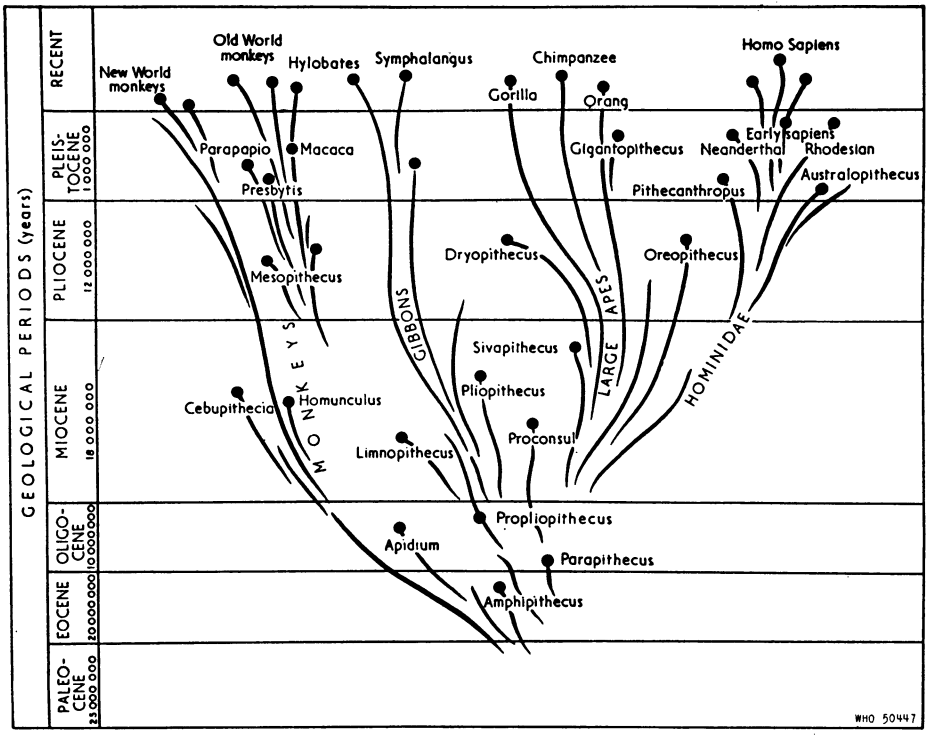
[a] Fossil sites are numbered as follows (South-East Asia sites not shown):

1. Clacton
2. Swanscombe
3. Abbeville
4. Markleeberg
5. Mauer
6. Torralba
7. Ternifine
8. Sidi Abderrahman
9. Mount Carmel
10. Soan River
11. Khor Aba Anga
12. Kamoa
13. Olorgesailie
14. Olduvai
15. Lake Eyasi
16. Makapan
17. Sterkfontein-Swartkrans
18. Taungs
19. Stellenbosch

[b] Water may mean a vast shallow lake.

FIG. 2

GENEALOGICAL AND EVOLUTIONARY RELATIONSHIPS OF THE SUBORDER ANTHROPOIDEA



Reproduced, by permission, from Harrison et al. (1964).

organisation into family and other units, effective system of communication, prolonged learning period of the young—was agonizingly slow and little is known about it (Leakey, 1961).

There is little doubt that during the second half of the Pleistocene the woodland savannah region of tropical Africa, with its lakes and rivers extending from the northern edge of today's Sahara to the southern tip of the continent, was the centre of the inhabited world and the fossil sites of Africa bear witness of this evolution (Fig. 1). Between two pluvial periods (the Kangeran and the Gamblian) the early men developed their tools from chipped pebbles to hand-axes, scrapers, spearheads and knives. Some penetrated into the thick forests but most of them remained in the open country, often near the lakes and rivers (Desmond Clark, 1959).

Paleolithic hunters and food-gatherers lived in small migratory groups of 20-60 people, returning to their shelters under rocks or in caves only for part of the year. The use of fire came late and followed a long sequence of earlier stone-age cultures covering at least 400 000 years.

It is obvious that each of these small human groups living in close contact with the teeming animal world interchanged with it their external and internal parasites. The infections were limited to the group of men and could not spread widely.

A drastic change occurred at the end of the Mesolithic period, when the domestication of plants and animals, followed by the concentration of large population groups started the Neolithic revolution (Childe, 1942). Surpluses became available for trading, mobility increased and with it the frequency of contacts, even when this meant war (Howells, 1960; Clarke, 1961).

Deevey (1960) pointed out that the human population, estimated at about 125 000 in the Lower Paleolithic, increased to over three million in the Upper Paleolithic (25 000 years ago). As a consequence of the expanded village farming, the human population went up from 5.3 million to

86.5 million during the short span of 40 centuries that separated the Mesolithic period from the time of the earliest known village community at Jarmo in Iraq (6500 B.C.). The relevance of this phenomenon to the study of crowd disease will become even more obvious when one realizes that the estimated world population density per square kilometre went up from about 0.04 during the Mesolithic to 1.0 at the time of the birth of Christ.

However, the striking possibilities of the gradual changes in host-parasite relationship of human infections will be better appreciated when we recall that over the past million years there lived a cumulative total of 110 thousand million individuals, of whom about one-third were Paleolithic men and the first tool-using Hominids (Deevey, 1960).

The human species that emerged from a number of related Hominidae by the beginning of the last glacial period (or perhaps earlier), some 100 000 years ago, and began to spread over most of the earth had probably already differentiated into three main stocks (Mongoloid, African, Eurasian), since racial differences are already present in human fossils older than 35 000 years (Howells, 1960). It is likely that the early prevalent human type in Africa was a proto-Bushman, and that he, together with the Negro, are the outcome of parallel evolutionary developments during the late Pleistocene. The Bushmen gradually moved away when the true Negro, who occupied the then well-watered area of the west-central savannah, spread over most of Africa during the past 10 000 years. By the third millenium B.C. this became the dominant group and the phenomenal speed of its cultural evolution has been revealed by the discovery of the over 3000-year-old terracotta figures of the Nok culture in Northern Nigeria (Oliver & Fage, 1962).

The fact that several closely related genera and species of the suborder Anthropoidea evolved in an ecological area in which the association with the existing insect vectors of various plasmodia was certainly close is suggestive of Africa as the original home of primate malaria; this was postulated by Christophers 30 years ago (1934).

Missiroli (1934) thought that the centre of evolution of "malariogenic Coccidia" was in Asia but that their final adaptation to the insect host took place in Central Africa and that from there the mosquito-borne infection moved gradually to the North.

The difficulties of paleo-epidemiology need not be stressed: absence of identifiable pathogens, unknown population figures, guessed-at environmental factors, unknown host or known only by fossil bones or mummified remains, uncertain geography, and obscure time factor (Cockburn, 1963).

The hypothesis of the African origin of malaria, however plausible on parasitological grounds, would gain a firmer basis if we had some data provided by circumstantial epidemiology (Macdonald, 1957), which normally precedes the etiological approach. It is true that even the concept of disease as a separate entity is modern, but in the case of some infections the symptoms are so definite that perhaps they could be traced far back.

The study of fossil or burial remains of prehistoric times showed that disease is as old as life itself and was prevalent before the advent of the human species. Ruffer (1921), Moodie (1923) and Pales (1930) devoted their pioneering studies to paleopathology of animals and men and the subject was fully reviewed by Sigerist (1951) and recently by Wells (1964). There is good evidence of the presence, long before historical times, of acute and chronic inflammatory diseases of bones, congenital defects, rickets, tertiary syphilis and other affections of the skeleton. Naturally much less is known about diseases of soft tissues but studies on several thousands of Egyptian mummies by Elliot Smith & Wood-Jones (1910) and, especially, by Ruffer (1912) showed evidence of tumours, pneumonia, pleurisy, urinary and biliary calculi, tuberculosis, smallpox, arteriosclerosis, and other affections.

The finding of *Schistosoma haematobium* eggs in the bladders of two mummies confirmed the description of haematuria recorded in the Ebers papyrus. As for the evidence of prehistoric malaria several large spleens were found by Ruffer (1921) in mummies of the first millennium B.C.; they might have been due to malaria or to intestinal bilharziasis or to some other affection and it is impossible to diagnose the disease with any certainty. Having examined hundreds of specimens from mummies, Ruffer (1921) never saw any remnants of red blood cells and was unable with chemical tests to obtain results positive for blood. On the other hand, the precipitin tests for human blood were frequently positive.

Recently, with the development of immunological techniques, it has been shown that blood-group determination of ancient tissues was possible (Smith, 1960; Springer & Williamson, 1960). There is evidence that in some conditions proteins may survive longer than was thought possible. Bone contains a considerable amount of proteins and if

blood antigens can be recognized after several hundreds of years, it is not unlikely that some other specific antigens could be demonstrated by means of sensitive modern techniques such as fluorescent-antibody tracing or haemagglutination tests.

It must be admitted that the study of the species distribution of human malaria parasites in Africa offers no clue for the explanation of the evolutionary history of this disease.

The virtual absence of *P. vivax* in West-Central Africa is just as puzzling as the peculiar distribution of *P. ovale* prevalent in this area but also found in East Africa. No convincing reason can be given for the patchy distribution of *P. malariae*, which occurs in all malarious areas but may reach in some foci a rate of 90%. The striking dominance of *P. falciparum* is related to environmental and ecological factors, including the easy transmission of this parasite by a number of anopheline species (Hackett, 1949).

In the course of the evolutionary history of parasites there must have developed a mechanism that maintains some balance between the parasite and the host and prevents the extinction of either. Such equilibrium due to a series of adaptations might have related to the chance of infection, to the virulence of the parasite and to the resistance of the host. The evolution of infection and defence discussed by Theobald Smith (1934) and admirably described by Burnet (1953) is of particular interest to us because of its bearing on the postulated origin of primate malaria on the African continent.

Malarial immunity has long been a subject of much discussion and an outline of this often controversial problem has been given by Sergent (1963) and by Taliaferro (1963). However, the innate or genetic aspect of the lesser susceptibility to induced as well as natural malaria infection of Africans or people of African stock has been given relatively little attention even though it has been suspected for nearly 80 years; Hirsch (1883-86) it was who said "the Ethiopian male, while having no absolute immunity, is still less affected than other races". This phenomenon was subsequently described by Koch (1898)[1] and by Stephens & Christophers (1900) and well summarized recently by Garnham (1963a).

The latter author admits that a genetic factor should be taken into account and Bruce-Chwatt (1963) stressed that some inherited resistance may appear after countless generations have been exposed to a ruthless process of selection as a result of which the capacity for a rapid response by the lymphoid macrophage system and the production of protective antibodies could be inherited. The relationship of a high degree of immunity to the long duration of asymptomatic low-degree parasitaemia still capable of infecting the vector is now better appreciated.

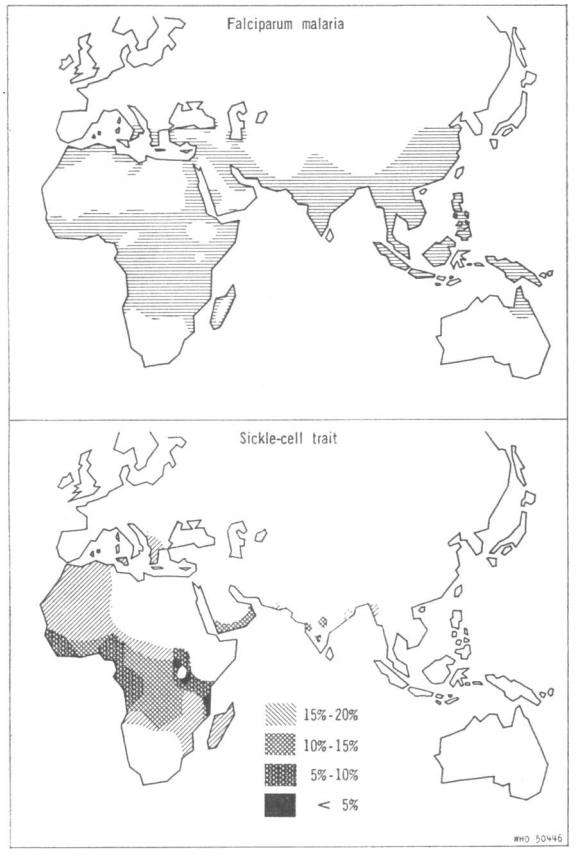
The degree of such innate relative resistance of the Negro race varies in relation to the species of the malaria parasite and is greater for *P. vivax* than for other human plasmodia. It is interesting, however, that it extends to other species of primate malaria. Coatney's (1963b) account of recent studies of simian malaria shows that the induced infection with several strains of *P. cynomolgi* by mosquito transmission or by blood inoculation to human volunteers was successful in 104 out of 122 Caucasians but failed in all of 11 Negroes.[2]

The capacity to develop an immune reaction may be regarded as a physiological attribute possessed by the human species as a whole and a product of evolutionary selection. Burnet points out that the type of immunity characteristic of man reflects his arboreal ancestry in tropical forest. Another type of resistance to disease results from genetically controlled characters not dependent on recent contact with disease. Haldane postulated that infectious disease should be regarded as an agent of natural selection of man in favouring the survival and reproduction of those individuals possessing genes making for resistance. Malaria is regarded as a prominent example of a disease with a genetic explanation of certain forms of resistance. There is evidence that the presence of haemoglobin S in a high proportion (5%-30%) of some populations may due to the selection of these genes by *P. falciparum* malaria. The partial protection against this infection afforded by the sickling trait increases the chances of survival of heterozygotes for the HbS gene and this type of balanced polymorphism may explain the striking correlation between the distribution of the HbS gene and that of *P. falciparum* in tropical Africa. Although the presence of this particular gene as a marker of past genetic connexions between various populations must be interpreted with caution; nevertheless, its widespread existence in Africa may indicate the effect of a long-term selective force of a disease with a special foothold on the African con-

[1] "*Es gibt sogar ganze Völkerschaften welche gegen Malaria immun sind. So glaube ich dies von den Negerbevölkerungen an der Ostafrikanischen Küste behaupten zu können*" (Koch, 1898).

[2] On the other hand the experimental infection of Negroes with *P. brasilianum* was successful (Contacos & Coatney, 1963).

FIG. 3
GEOGRAPHICAL DISTRIBUTION OF *P. FALCIPARUM* MALARIA AND OF SICKLE-CELL TRAIT IN THE OLD WORLD



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tinent (Fig. 3) (Allison, 1961, 1963; Harrison et al., 1964; Motulsky, 1960, 1964).

One takes no great liberty with historical truth in assuming that prehistoric man, at least in some warmer regions, must have been an early victim of malaria (Russell, 1955) and that, as a consequence, he developed some resistance to it.

THE SPREAD OF HUMAN MALARIA TO OTHER CONTINENTS

While it is presumed that Africa was the cradle of malaria, nothing is known about the geography of this disease, which was undoubtedly encountered by the ancient explorers of Africa. The contacts of the ancient centres of civilization with tropical Africa were astonishingly wide and must have played an important part in the spread of malaria. It has been pointed out (Alimen, 1955; Deschamps, 1962) that one-third of human remains in Egyptian predynastic tombs and all the prehistoric rock paintings at Tassili in the Sahara are of Negro type.

About 3000 B.C., Snefru, the King of Egypt, raided the Ethiopians of Nubia; at the time of the twelfth dynasty (2000 B.C.) settlements of Egyptians existed near Wadi Halfa and from about 1000 B.C. they went as far as the Bahr el Ghazal and even beyond it. From then on the Greeks, Persians and Romans explored Ethiopia and East Africa and in the third century B.C. Diogenes the Greek, shipwrecked on the East African coast, had probably been to Kenya, Uganda and Tanganyika. Herodotus reveals that the Sahara was crossed from Cyrenaica by the Berbers and Carthaginians and the military expeditions of the Roman generals Balbus, Flaccus, Maternus, Suetonius in the first century A.D. reached Timbuktu and Lake Chad. In the year 600 B.C. the Phoenicians, sent by Necho, a king of Egypt, circumnavigated Africa from east to west; a century later Hanno sailed as far as today's Sierra Leone, where he landed. Pottery found recently in the Bosumpra cave in Ghana shows clearly its connexions with the Kingdom of Meroe in the Sudan (500 B.C.). There were other voyages to or around Africa before the Christian era, such as that of Satarpes the Persian and Eudoxus the Greek, and probably many attempts that were never described (Cary & Warmington, 1963).

Five thousand years ago the predynastic Egyptians visited the lands of the Persian Gulf; the Sumerians landed on the shores of the Red Sea, the Phoenicians in India and along the East African coast. Three thousand years ago the Greeks knew the whole of the Mediterranean and went far beyond it; the Persians, Greeks and Romans went to India, Ceylon, China and Indonesia. With the retirement of the Romans the Chinese came sailing as far as the Persian Gulf and the East African coast from Mombasa to Dar es Salaam. The Malayan colonization of Madagascar is a striking example of the antiquity of human movements some 4000 miles away from the nearest possible starting-point. These movements were not limited to small groups of sailors; huge waves of overland invasions moved over Europe, Africa and Asia (Johnston, 1937).

There is little doubt that one of the greatest steps in human civilization—transition from a food-

gathering to a food-producing economy—related to the invention of agricultural tools, the development of social life, travel and increase of the size of settled human groups must have been of paramount importance to the epidemiology of communicable disease (Sigerist, 1951; Burnet, 1953). A recent study of the origin of the treponematoses (Hackett, 1963) gives an excellent example of this thesis.

Any attempt to outline the early history of malaria is bound to be speculative and could be given the name of stichomancy—divination by means of passages in books.

Many prehistoric data on the epidemiology of malaria have been given in general histories of medicine. Among the authors dealing specifically with the antiquity of malaria infections Jones (1909), Ross (1911), Celli (1925), Knowles & Senior-White (1930), Hoops (1934), Boyd (1949), Russell (1955), Hoeppli (1959), Singer & Underwood (1962) must be mentioned and their works still constitute our main source of information.

The consensus is that in prehistoric times malaria was very common in the upper valley of the Nile, accessible from the vast hinterland of tropical Africa, but relatively rare in Northern Egypt (Russell, 1955). As mentioned before, enlarged spleens possibly due to malaria have been found in mummies about 3000 years old and splenomegaly with fever is mentioned in the Ebers Papyrus of 1570 B.C. (Ebbell, 1937).[1] However, although the range of clinically recognizable diseases in the Egyptian medical documents is truly astonishing (Major, 1954), there is no clear description of malaria in the papyri translated until now (Hoeppli, 1959). The oft-quoted reference to the "AAT disease" of an inscription in the temple of Dendera as pertaining to malaria is now doubtful (Ghalioungui, 1963). Herodotus and Diodorus were impressed by the good health of the ancient Egyptians, although in some places mosquitos were so abundant that (according to Herodotus) fish nets were used for protection against bites.[2] Magic and religion were inseparably connected with treatment by foul substances given to the patient as part of the spell and this might be the beginning of empirical therapy when association between cause and effect was observed.

Mesopotamia, the land lying between the Euphrates and the Tigris, which gave rise to the Sumerian and then Babylonian, Assyrian and Chaldean cultures some 3500-3600 years B.C., must have been, judging from its geographical situation, one of the important malarious areas of the ancient world. Mentions of deadly fevers and of intermittent fevers affecting many people at the same time are frequent in the 800 clay tablets referring to medicine and surgery which form a part of tens of thousands of tablets in cuneiform writing found in the library of Ashur Banipal and dating back to 2000 B.C. Only a small proportion of this Sumerian text has been deciphered (Sarton, 1959).

A votive object found at Susa bears an incantation against mosquitos: it is a cylinder seal with a symbol of a fly, the emblem of Nergal, the Babylonian god of disease and death (Garrison, 1929). The Old Testament and the Talmud contain a mass of information about the Hebraic medicine and sanitation, but there are very few references to fevers that could possibly be malaria (Preuss, 1911; Short, 1953).

It is generally agreed that for thousands of years before recorded history large areas of India suffered from a number of epidemic diseases, including malaria. The people of Mohenjo-Daro and Harappa, contemporary with the old kingdom of Egypt, developed in the Indus valley a flourishing civilization, as shown by their remarkable urban planning and water disposal. However, in the deltas of this subcontinent's large rivers, malaria must have been rife, as may be surmised from many references to deadly fevers found in the writings of the Vedic (1500-800 B.C.) and the Brahmanic (800 B.C.-A.D. 100) periods of Indian medicine.

Russell (1955) points out that the Vedic medical teaching referred to autumnal fevers as "king of diseases" and described the enlargement of the spleen. An incantation from the Atharva-Veda addressed to Takman, the fever-demon (Muller, 1937) anticipates the Hippocratic description of the symptoms and the periodicity of malarial attacks by about 600 years.[3] The early Ayurvedic sages Charaka and Susruta both noted the tertian and quartan fevers (Raina, 1951) and Susruta's observa-

[1] "If thou examinest a man with a resistance in his left side and it is under his flank and does not cross the earth [? stretch across the abdomen] then thou shalt say of him: it has produced [like ?] a shore and formed a s'jt cake" (Ebbell, 1937).

[2] "Those living about the marshes have a net with which they catch fish by day and for the night they set it round the beds where they rest and then creep under it and so sleep" (Sigerist, 1945).

[3] "To the cold Takman, to the shaking one, and to the deliriously hot, the glowing, do I render homage. To him that returns on the morrow, to him that returns for [?] two successive days, to the Takman that returns on the third day homage shall be." (Sigerist, 1951).

tion that malaria may be carried by mosquitos (*masakah*), of which there were at least five kinds, has been referred to by Russell (1955).

Malaria was known in China long before the beginning of the Christian era. The Chinese medical classic *Nei Ching* (The Canon of Medicine), edited in 2700 B.C. by the Emperor Huang Ti, mentions the enlargement of the spleen connected with different types of fevers. Together with exorcisms, acupuncture, moxibustion, etc., various plant remedies were used by the Chinese physicians, including Ch'ang Shan (*Dichroa febrifuga*), which has some antimalarial properties. Among 16 " kinds " of malaria recognized by the old Chinese medicine two are of particular interest: Yi-Yao, or epidemic malaria; and Yao Mu, " mother of malaria ", referring to repeated paroxysms and large spleen (Hoeppli, 1959).

The dawn of Greek history about 1600 B.C., linked with the invasions of various tribes, brought southern Europe and Asia Minor into close contact.

The Iliad of Homer, dating back about a thousand years B.C., mentions the presence of autumnal fevers (Russell, 1955) but not all authors agree that they were due to malaria. Jones et al. (1907) and Jones (1909) believe that malaria began to spread in Greece several centuries later and especially after the Peloponnesian war. Sigerist (1960) summarized about 70 cases of various afflictions listed in votive tablets left by grateful patients in the Asklepeion at Epidauros in the sixth century B.C. and none of these refers to recurring fevers.

Livadas (1959) stressed the fact that the early Greek mystic poems once ascribed to Orpheus and written probably at the end of the 6th century B.C. clearly describe the symptoms of intermittent fevers and the long duration of the quartan form.[1] This would confirm the view that epidemics of malaria became frequent at that period, having spread to Greek cities from Egypt and Sicily (Jantsch, 1948).

Only after 500 B.C. did the disease become endemic throughout the greater part of the Greek world and it was probably responsible for its downfall (Jones, 1909).

The paramount importance of Hippocrates in the history of malaria need not be stressed. Living in the fourth century B.C., he must have seen a number of cases and his superb description of various fevers (Epidemics, I, 24; Aphorisms, II, 25) removed from the phenomenon of disease the supernatural element. The incomparable treatise on " Airs, waters and places " is the first approach to epidemiology and medical geography as we understand it today.

There is no evidence that malaria was a public health problem in Italy among the ancient Etruscans, but it became endemic about 200 B.C. and was quoted often in Roman medical and philosophical literature. The practical approach of the Romans to problems of public health can be seen in their successful attempts at draining marshes, recognized as a source of the disease (Ross, 1911; Russell, 1955). The whole history of malaria in Italy was dealt with by Celli (1925).

The antiquity of human malaria in the Old World is firmly established. It seems that it must have originated in tropical Africa at the dawn of humanity and was self-contained in small foci during the Paleolithic and Mesolithic periods. With the Neolithic revolution, followed by the increase in the settled human groups and in the mobility of man, the infection spread and established itself in the great centres of riverain civilizations in Mesopotamia, India and South China and in the Nile valley, from which it invaded the Mediterranean shores. From these five main foci malaria extended its hold over most of the tropical world and much of the land in the temperate climates (Fig. 4).

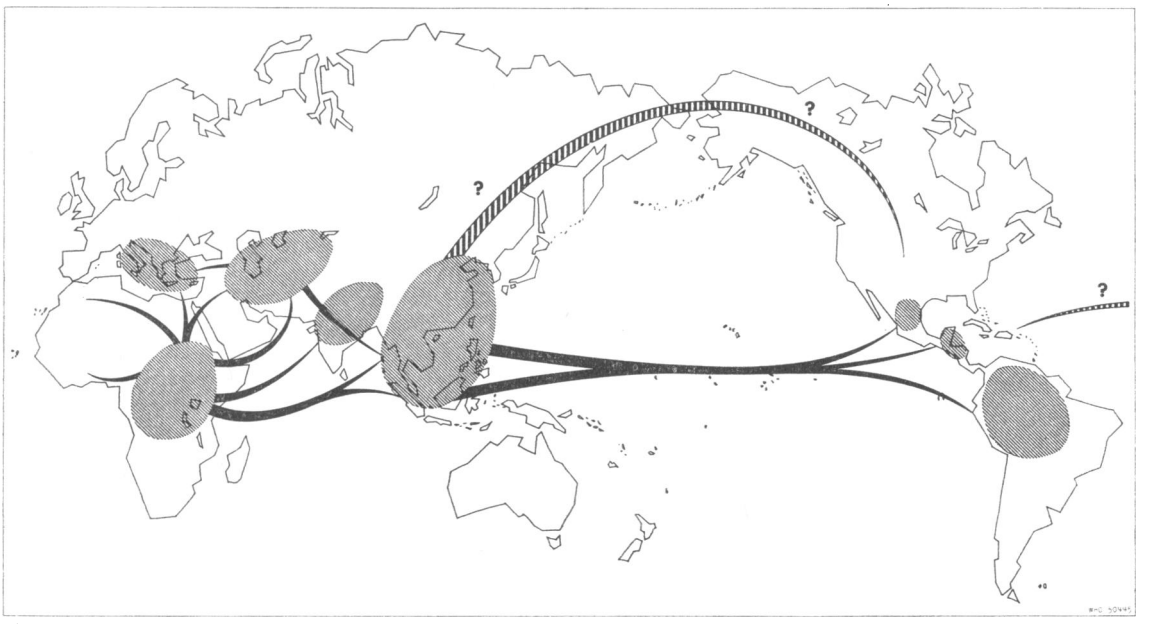
MALARIA IN PRE-COLUMBIAN AMERICA

The presence of malaria in the New World is much more difficult to explain and subject to even greater speculations (Boyd, 1930). Two schools of thought exist at present. Carter (1931), Netolitzky (1932), Scott (1939), Boyd (1949), Jarcho (1964) and others believe that malaria in the Americas is a post-Columbian importation by Spanish conquistadors and later by the colonists; the infection carried by local *Anopheles* spread from the island of Hispaniola to other islands and from there to the mainland. In a remarkable and too little known study Ashburn (1947) gathered much valuable information in defence of this opinion and stressed the importance of the African slave-trade in the introduction of malaria from the Old World into the New.

Another group of historians with a good knowledge of Central and South America—particularly Flores (1886), Barbieri (1910), Penna & Barbieri (1916), Arcos (1938), Paz-Soldán (1938), Jaramillo-

[1] " If a blazing fever comes to a man on alternate days or if a fever with chill gets hold of him, he will not be able to use his limbs. But if he is afflicted by the slow misery of a four-day fever it will remain with him for a long time as this [sickness] is not cured by the noble agate-stone. Of all the fevers this one lasts longest " (*Orphics, Lithica* (On the properties of stones), verse 627; translated by P. Issaris).

FIG. 4
PROBABLE ROUTES OF SPREAD OF MALARIA IN PREHISTORIC AND EARLY HISTORIC TIMES



Arango (1950) and lately Hoeppli (1959), Guerra (1964) and others—take an opposite view, believing that malaria existed in Central and South America long before the arrival of the Europeans. Discussions related to the question of the pre-Columbian existence of malaria are based on three types of evidence: (*a*) linguistic, (*b*) botanical and (*c*) historical.

Before commenting on some of these arguments it might be useful to recall that pictures of mosquitos were found on prehistoric pottery from New Mexico and that Bernal Díaz del Castillo ([1632]) often refers to the plague of mosquitos which made life difficult in several places on the Mexican Coast.

The linguistic evidence of the antiquity of malaria in today's Mexico and Central America dates from Alonso de Molina (1571), who, in his dictionary of the Mexican language, translates the Nahuatl word *uiptlatica atonauiztli* as *calentura con frío*. This is quoted by Flores (1886) as meaning tertian fever.

Guerra (1964) in his study of Maya medicine stresses that the Maya had definite names for symptoms such as malaise (*cunulba*), headache (*kuxpolil*), chills (*yaxcél*), and fever (*chacanil*). A number of medical terms are given in a Maya lexicon by the Friar Pedro Beltrán which summarizes the knowledge existing at the time of the Spanish conquest. Among 200 terms for various symptoms and diseases, Beltrán mentions *camsackin* and *yaxceel*, two names that may refer to malaria. They are different from the name of a febrile disease with black vomit (*xekik*) that could mean yellow fever, a disease which, according to Guerra (1964), must have been known in pre-Columbian America as it is mentioned in Maya codices about A.D. 1350.

Markham (1908), Barbieri (1910), Vaughan (1923) and Lastres (1951) pointed out that some Indian vocabularies of Peru contain native words for a disease characterized by symptoms of chills and fever (*chuchu*, *chucho*, *chucha*). Guerra (personal communication) states that *chucchu* (also *chucchu-capa* or *chucchuhuni*) was translated from the Quechua of the Incas by González Holguín (1608) as *tertiana calentura* or *frío de calentura*. Even before that date Father Domingo de Santo Tomás in his Quechua vocabulary of 1560 translated *chucchu* as " chill and fever " (Jaramillo-Arango, 1950). The first reference to *chucchu* is ascribed to Garcilaso de la Vega (the son of a Spanish noble and an Inca of royal descent), who connects it with intermittent fevers and incriminates the rigor (*chucchu*) followed by fever (*rupa*) as the cause of death of the Inca

King Huayna Capac in 1527.[1] However, other authors believe that the death was due to smallpox and Ashburn (1947) thinks that the two terms refer to Oroya fever, but Alvarado (personal communication) supports the view that *chucchu* was a native term for malaria.

Botanical evidence is also of uncertain character. The therapeutic virtues of the cinchona bark are believed to have been known to the native Indians of Peru, who confided their knowledge to the Jesuit missionaries after the conquest of the country by Pizarro in 1527. Anton Bollus, who lived in Peru for many years in the seventeenth century, de Jussieu and La Condamine, who visited Ecuador in 1735-39, and William Arrot, a Scottish surgeon who went to Peru at about the same time, affirm that the cinchona bark was well known to the Indians and that they used it for treatment of fevers (Wellcome, 1930; Jaramillo-Arango, 1950). And yet a number of naturalists and explorers and among them the Ulloas (1748), Humboldt (1821) and Markham (1880), emphasized that there is no reference to the cinchona plant in the available written records of Incas, Mayas and Aztecs. This would imply that malaria was unknown in America before the Spanish conquest and such a view has been upheld by Carter (1931), Netolitzky (1932), Ashburn (1947), Ackerknecht (1948) and others. There is no mention of the cinchona trees (which grow in large thickets near Quito) in the Spanish diaries and chronicles from Peru, such as the illustrated volume by Poma de Ayala written in 1587 or other books by Polo de Ondegardo, Cieza de León, Sarmiento de Gamboa and Pedro Pizarro. Prada (quoted by Paz Soldán, 1938) maintains that the Peruvian Indians knew the use of cinchona bark and supports his opinion by references to the contemporary writings of Garcilaso de la Vega [1] and Fathers Antonio de la Calancha and Bernabé Cobo.

Arcos (1938) believes that the use of the bark was known by two tribes only (Paltas and Zaraguros) and Jaramillo-Arango (1950) upholds the view of the pre-Columbian knowledge of cinchona at least among some peoples of Peru. The latter author gives the history of the introduction of the cinchona bark into Europe, explains the confusion regarding the indigenous name of the tree (*quina-quina*) and outlines the fundamental errors in the early history of cinchona described by Paz Soldán (1938) and by Haggis (1941).

It is certainly puzzling that not one of the various preserved codices from Mexico (see Soustelle, 1950; Mason, 1961; Vaillant, 1961) contains the description of the use of the " fever bark ". There is no mention of it in the Spanish chronicles of Bernal Díaz, las Casas, Gomara, Herrera, Oviedo, Sahagún and others. The only oblique reference to a herb called *chichic-patl* that is " good for intermittent fevers " comes from Francisco Hernández, the court physician of Philip II, appointed in 1570 *protomedico de las Indias*, where he remained for seven years. Part of Hernández' manuscript was destroyed by fire in the Escurial but the remainder was published and annotated (Hernández, 1615). Ashburn (1947) has doubts about the value of this evidence. However, the negative argument is perhaps less important if one remembers that many Aztec and Maya manuscripts in hieroglyphic writing have not been deciphered and that a large number of written records found in Mexico were burned in 1562 at the order of the pious bishop Diego de Landa (Guerra, 1964).

Prescott's *History of the conquest of Peru* (1847), the most informative, balanced and well-documented narration of a crucial phase in the history of the New World, is singularly disappointing for a medical historian. It is probable (as Seccombe points out in the preface to the 1907 edition) that in the course of severe pruning of his first text based on Spanish chronicles Prescott discarded all the facts that were irelevant to his major theme.[3]

[1] " *Al frio de la terciana o cuartana llaman Chuchu, que es temblar ; a la calentura llaman Rupa, que es quemarse ; temían mucho estas tales enfermedades, por los estremos ya de frio ya de calor* "; Garcilaso de la Vega (1723), lib. II, cap. XXIV.

[2] " . . . *grandes herbolarios que los hubo muy famosos en tiempos de los Incas que conocían la virtud de muchas yerbas... De otras muchas yerbas usaban los Indios mis parientes de las cuales no me acuerdo* . . . "; Garcilaso de la Vega (1723), Libr. II).

[3] Prescott's description of Gonzalo Pizarro's and Orellana's expedition in 1540 from Quito over the Andes to the Amazon contains a curious statement obviously gleaned from chronicles of Herrera, Garcilaso, Gomara, Montesinos or Gárate: " After some months of toilsome travel, in which they had to cross many a morass and mountain stream, they at length reached *Canela*, the land of Cinnamon. They saw the trees bearing the precious bark spreading out into broad forests; yet however valuable an article for commerce it might have proved in accessible situation, in these remote regions it was of little worth " (from the 1907 edition, book IV, chapter 4).

The reference to " Canela " or cinnamon is certainly in error. True cinnamon (*Cinnamomum zeylanicum*), one of the oldest known and most coveted spices, is an indigenous tree of Ceylon and South India though some species grow also in Burma and Malaya. The canella-bark (*Canella winteriana*), or " white cinnamon ", grows in the West Indies or coastal areas of South America but not on the Andean slopes

[*continued overleaf*]

The historical evidence for and against the pre-Columbian existence of malaria in the New World is equally if not more controversial. Those who deny it (Carter, 1931; Netolitzky, 1932; Scott, 1939) stress the absence of clear references to epidemics of fevers, but Penna & Barbieri (1916) and Hoops (1934) believe that the medicine-men of the Incas were acquainted with the disease while Arcos (1938) states that it affected the armies of Pachacuti in 1378. Boyd (1930), in assessing the conflicting claims, points out that the febrile disorders cannot be differentiated from other contagious diseases and leaves the question unanswered. Nevertheless he agrees that malaria might have been responsible for the early misfortunes of the Spanish colonists.

Whether the sickness that fell within a few weeks on one-third of the men of the first Spanish settlement at Navidad was malaria or not cannot be determined but this did not prevent Columbus from founding in 1493 on the island of Hispaniola a second, larger settlement of Isabella. This was a wretched and mutinous community suffering from outbreaks of various diseases, probably because of the close association between the settlers and the groups of Indians assigned by force to every settler. Within a few years Isabella had to be abandoned and the remaining colonists went to the mainland (Morison, 1924; Pendle, 1963).

The isthmus of Panama (Castilla del Oro) discovered in 1501 had its first Spanish settlement of Nombre de Dios only in 1509, and from the beginning the colonists suffered from various " fluxes and fevers " and particularly the " Chagres fever ", which might have been anything including yellow fever or malaria but was so fatal that this port for royal galleons was given the name *sepultura de vivos* and later had to be abandoned (Simmons, 1939).

Ashburn (1947) does not believe that the sickness of the early colonists was due to malaria, and stresses that neither the medical account of Chanca, the physician to the fleet on Columbus' second voyage, nor the later chronicles by Oviedo, Herrera, Sahagún,[1] Bernal Díaz del Castillo, Gomara and others provide any incontrovertible proof of epidemic fevers and points out that the high mortality might have been due to starvation, scurvy, dysentery, typhoid, etc.

Although Reko (1931) stated that amoebic dysentery, leishmaniasis and malaria were known to the Aztecs and Mayas and that the Spanish conquerors including Cortez and Bernal Díaz suffered from the latter disease, particularly during their march to Honduras, the factual evidence for it is slim.

It is obviously impossible today to diagnose with any certainty all the various diseases which decimated the Spanish and Portuguese conquerors of the New World. A fatal condition known as *modorra*, observed during Balboa's 1513 expedition across the Isthmus and Pedrarias' settlement in 1514 at Darien, was probably " Oroya fever "—a bartonellosis—although Andagoya, a member of the expedition, stresses the swampiness of the site. It is not unlikely, however, that malaria was responsible for Don Diego de Ordaz losing 300 men during his exploration of the Orinoco river in 1534; heavy losses were also sustained by the Spanish force under Jiménez de Quesada sailing up the Magdalena river in today's Colombia; the same deadly fevers decimated the army of Don Pedro de Alvarado in 1534 when crossing the tropical forest of the coastal area in today's Ecuador. On the other hand, the 1541 expedition of Gonzalo Pizarro taken over by Francisco de Orellana travelled for eight months along the Amazon river but the available records make no reference to fevers that could be interpreted as malaria. Neither does Magalhães, who in 1570 travelled through the " Province of Santa Cruz ", which is the coastal area of today's Brazil.

The early explorers of today's southern states of the USA (Ponce de León, Pánfilo de Narváez, Hernando de Soto) described their great losses but gave no specific indication that these were caused by

crossed by the expedition. It is not likely that the trees mentioned by Prescott are the " Peruvian balsam tree " (*Myroxilon peruiferum*) which has previously been confused with cinchona; as in the case of " white cinnamon " the myroxylon trees would not be found in the area and at the altitude mentioned by Prescott.

On the other hand, the cinchona is found along the eastern slopes of the Andes, growing at the altitude between 2500 and 7500 feet (about 750-2250 m) in regions of abundant rainfall. The bark of some cinchona trees is brownish-red and this might explain the mistake of the Spaniards looking for cinnamon trees. It is probable that the " precious bark " was that of cinchona and that Prescott either misinterpreted a passage in the original Spanish chronicles of the conquest of Peru or that the true purpose of the bark was not realized by the authors of the chronicles, though its value must have been known to the Indians. As in other instances, this point illustrates the need for a serious study of original old Spanish and Portuguese chronicles to gather some still undiscovered facts of importance to the medical historian.

[1] Ashburn (1947) quotes an unpublished study of Dr Ignacio Alcocer from Vera Cruz, who commented on medical data in Sahagún's work. It appears that Sahagún mentioned " fevers with chill ", " fever of the country ", but those references are too vague to be of much help in identifying malaria.

a well-defined disease. Clear evidence of malarious conditions in Virginia dates only after 1600, but not until the eighteenth century did malaria become widespread in that area. The French Huguenot settlements in Florida suffered not only from starvation but also from fevers from their early days (Laudonnière, 1853).

Ashburn (1947) emphasizes that malaria must have been introduced into the New World from the early days of the Spanish conquest by Negro slaves, and Jarcho (1964) believes that an endemic focus of malaria at San Sebastian de Urabá reported by Fernando de Oviedo could have been established in Panama by the Spaniards who visited this area previously and were accompanied by Negro slaves.

Although the first Africans may have been brought to the islands of Cuba and San Domingo as early as 1503, their numbers were relatively small and it is most doubtful whether any large-scale epidemics of malaria could have started so soon from these probable carriers of plasmodia. By 1510 the Negroes were in great demand by their Spanish masters to replace the rebellious Indians and after 1514, when Bartolomé las Casas, the Bishop of Mexico, began to denounce the cruelties inflicted on the Indians and proposed that Negro slaves should replace them, Africans were shipped across the Atlantic in ever-increasing numbers. By 1576 there were some 40 000 in Spanish America alone and during the seventeenth and eighteenth centuries the annual number of imported slaves often exceeded 100 000. The total number of slaves in all European colonies of the New World has been estimated as high as 40 million (Coupland, 1933) and the social, political and medical impact of this infamous chapter of history cannot be overstressed (Scott, 1939).

Any discussion of the evidence for or against the existence of malaria in pre-Columbian America suffers from all the uncertainties that have been described by Scott (1939) with regard to the problem of the origin of yellow fever and the confusion between these two infections adds to the difficulty of any conclusion. Various arguments can be marshalled on either side and for the time being no linguistic, botanical or historical facts can help to answer the question to everybody's satisfaction.

It is interesting to note that while the available historical documents fully support the suggested European origin of smallpox and probably measles, introduced into the New World by the colonizers and evidenced in the form of epidemics which decimated the local populations (Nicolle, 1933), there is no similar information about other fevers (including malaria) being more deadly to the indigenous inhabitants than to the Europeans. In 1530 the Aztecs lost nearly half of their population from smallpox (Soustelle, 1955). The absence of a similar occurrence with regard to malaria may be used as an argument that this infection must have been present in pre-Columbian America and that the Indians had a degree of immunity to it. Oviedo mentions the high mortality of the Indians and the gradual depopulation of the island of Hispaniola, but ascribes it to hard work and ill-treatment without mentioning any febrile disease.

It should be remembered, however, that the Portuguese voyages to West Africa in the fifteenth century yielded no clear records of yellow fever (a much more striking disease) among the explorers and this shows the frailty of negative evidence.

Following the discovery of Brazil in 1500 by Pedro Cabral the Spaniards and the Portuguese conquered and partly occupied within 50 years a huge area of the Americas stretching from Mexico through Peru to Uruguay. There are few studies of the medical problems of this unprecedented colonization of two continents by Europeans. Little attention has been given to careful sifting of the medical facts scattered in the chronicles quoted before and in many others too numerous to mention. It is hoped that medical historians will investigate this fascinating subject, even though the results may not provide any more factual data than those available now.

Summing up the evidence, Russell (1955) says wisely that if malaria existed in the Americas before Columbus it must have had a patchy distribution. This is even more likely if one considers that the main American indigenous civilizations were on the mountain plateaux and high valleys with a salubrious climate, so that only the coastal areas may have been malarious.

Alvarado (personal communication) strongly supports this view and stresses that the indigenous inhabitants of Peru, Bolivia and Ecuador developed remarkable systems of irrigations situated mainly in the highlands and that they avoided the potentially fertile land in low-lying, probably malarious areas. Jarcho (1964) stated that the presence of malaria in pre-Columbian America is improbable but not impossible. It seems, however, that an increasing number of people would agree that this statement is too exclusive and that the appropriate term would be " probable but not proved ".

Most of the references to malaria in pre-Columbian America understandably fail to distinguish between the different species of parasites. It is likely that *P. vivax* and *P. malariae* existed in several areas of Central and South America before the discovery of the New World and that *P. falciparum* was brought by the Spaniards and their Negro slaves.

If it is accepted that malaria existed in the Americas before Columbus the answer as to the way the infection came to the New World from Asia is difficult. The basic concept that man came into the New World fully evolved is generally accepted though the early man in the Americas has now been given a tenure of 40 000 years (Jennings & Norbeck, 1964). This would account for profound cultural changes of the descendants of Asian hunting tribes who, during the late Pleistocene, crossed the Bering land bridge in pursuit of animals. Progressing slowly southwards down the American continent, they divided into small groups and developed, in isolation, a multiplicity of cultures (Clarke, 1961; Vaillant, 1961).

One must agree with Cockburn (1963) that the survival of malaria parasites in man or vectors during the thousands of years of the post-glacial period is most unlikely; if the original inhabitants of the American continent were free of malaria, the infection must have been introduced relatively recently, though long before the landing of Columbus.

Even without invoking the ghost of the legendary Atlantis as a stepping-stone from the Old World to the New, there is evidence of prehistoric voyages of peoples of the Bronze Age who lived on the western shores of the Mediterranean and sailed over the Atlantic perhaps as far as the coast of Central America. The Azores and the Canaries were inhabited by stone-age populations and a hoard of Carthaginian coins of the fourth century B.C. has been found on one of the islands of the Azores over 800 miles from Portugal, the country whose sailors did not discover the archipelago until 17 centuries later (Bibby, 1962).

It is likely that this confirms the story about the Atlantic voyages of Himilco, the Carthaginian captain, of Pytheas the Greek, and of others (Cary & Warmington, 1963).

Jeffreys (1953) believes that Arab navigators and slave-traders had made repeated contacts with the Caribbean coast of America about 900 A.D. and supports this statement by botanical, anthropological and historical data. Recently this possibility has been supported by Hui-Lin-Li (1960), who provided additional evidence of transatlantic travels of Arab mariners from the study of Chinese geographical documents of the twelfth century.

More is known today about Norsemen who had a short foothold in North America at the end of the first millennium A.D. and whose definite traces have just been discovered in Newfoundland (Ingstad, 1964).

However, it appears that the pre-Columbian contacts of the New World with the Old were more likely across the Pacific Ocean and this idea is now increasingly accepted by many anthropologists (McNeill, 1963). There are too many cultural and other resemblances between the indigenous civilizations of mainland America and those of Polynesia, Melanesia and South-East Asia that are impossible to account for on other grounds than prehistoric contacts (Clarke, 1961). The evidence indicates voyages across the Pacific at several different times and on several different horizons, some of them surprisingly early but others as late as the first millennium A.D. (Mason, 1961; MacGowan & Hester, 1962).

The Kon-Tiki expedition showed that primitive people could undertake immense voyages over the open sea. Although the winds and currents in the Pacific are normally in the westward direction the equatorial belt offers better sailing conditions for a stage-wise progress from one island to another and the probability of repeated voluntary or accidental (storm-driven) migrations from South-East Asia to Central and South America must be taken into account when we discuss the prehistoric epidemiology of infectious disease in the New World. This, Captain Cook's theory of 1784, has now been given full support by Sharp (1957).

Candau (personal communication) stresses the fact that the western coastal areas of South America had originally a higher degree of malaria endemicity than the ecologically comparable areas inland or on the eastern shores of the continent. Da Fonseca (personal communication) believes that several mycotic, helminthic and protozoan diseases were imported into the Americas from Polynesia, Micronesia and Melanesia and does not exclude malaria from this group.

The attempt to study " through the glass darkly " the ancient history of a disease that leaves no trace in human remains is so bold as to be foolish. The circumstantial and speculative approach used

may not be the ideal but it is the only one possible when our knowledge is still so meagre and so fragmentary.

However, recent excavations in Mexico, Peru and the USA may perhaps provide a factual clue not only to archaeological but also to some epidemiological problems. In 1925 the Peruvian archaeologist Tello discovered in the north of Peru 400 mummies belonging to the Chavin culture that flourished 3000 years ago. Many more sites with mummified remains have been found elsewhere in the Americas, including the states of Arizona, Colorado, New Mexico and Utah of the USA. They all belong to various cultural periods centuries before the first landing of Colombus in the New World. If chromatographic techniques as used by Abelson (1956) could show the presence of amino-acids in fossil clam shells 300 million years old, it can be hoped that the modern immunological methods used for study of the mummified remains of ancient inhabitants of America may solve the tantalizing riddle of the early history of malaria. It is hoped that this advance of our knowledge is not too far away, even though Cockburn (1963) says that in the field of epidemiology an antibody has as much relation to the antigen as the photograph to the original document and that it constitutes good but not final evidence of the infection.

CONCLUSION

Recapitulation of the paleo-epidemiology of malaria shows once again that history and geography of disease are inseparable and it emphasizes the concept that man is only one-half of the reactive system while the other is his environment, full of dangers but also of stimuli that challenge man's ability to survive (May, 1958, 1961). There are few diseases that show this concept as well as malaria does and an African poet, Léopold Sedar Senghor, invoking " *Toi, calme Déesse au sourire étalé sur l'élan vertigineux de Ton sang. O Toi impaludée de Ton lignage . . .* " expressed it in words that are deeply moving. Sherrington (1940), who saw the plasmodial infection as one of the striking products of evolution, used it as an example in discussing the ethical principle of nature and in absolving her from either good or evil designs. In stressing that the human mind faced with nature has no appeal and no resort for help beyond itself, Sherrington taught us a lesson that we should remember: " Ours is the situation . . . which elevates the spirit to the position of virility and dignity which otherwise man could not possess. We have, because human, an inalienable prerogative of responsibility, which we cannot devolve even upon the stars. We can share it only with each other."

RÉSUMÉ

Dès le début de l'étude des Hémosporidies, les parasitologistes ont été frappés de la similitude entre le cycle d'évolution de ces parasites et celui d'autres parasites intestinaux appartenant à l'ordre des Coccidiés. Les Hémosporidies peuvent être considérées comme des Coccidiés de l'épithélium de l'hôte vertébré qui, peu à peu, se sont adaptés, d'abord à certains tissus des organes internes, et ensuite à la vie à l'intérieur des cellules mobiles du sang. Il est probable que les parasites du paludisme sont issus des Coccidiés par l'intermédiaire de parasites du type hémogrégarine.

L'hypothèse selon laquelle les plasmodiums seraient apparus d'abord chez les insectes, puis chez les vertébrés n'est pas confirmée. Le fait que les Hémosporidies se soient mieux adaptées aux insectes — comme le prouve l'absence apparente de pathogénicité pour l'hôte invertébré — n'est pas considéré, suivant les normes de l'évolution, comme un argument probant.

Le commensalisme a-t-il précédé le parasitisme, ou bien est-ce l'inverse ? Il est impossible de donner une réponse générale. Le parasitisme peut prendre naissance de diverses façons dans des groupes d'animaux différents: chez certains, il peut être précédé d'une certaine forme d'association; chez d'autres, il peut se manifester dès le premier contact avec l'hôte. Dans les deux cas, les facteurs biocénotiques ont une influence considérable sur l'apparition du parasitisme.

D'une manière générale, on considère que le genre *Hepatocystis* et le « groupe quarte » des Plasmodiums représentent les plus anciens des parasites du paludisme. Viennent ensuite ceux du « groupe tierce ». Le sous-genre *Laverania* est probablement le plus récent.

Notre connaissance des parasites du paludisme des singes s'est considérablement accrue pendant les cinq dernières années.

L'extrapolation au paludisme humain des progrès dont a bénéficié depuis peu notre connaissance du paludisme simien doit être prudente. Cependant beaucoup de conclusions des primatologistes viennent confirmer le fait non discuté d'une association de longue date entre les parasites du paludisme et les ancêtres de l'homme.

Le fait que l'évolution de plusieurs genres et espèces d'anthropoïdes s'est effectuée dans une région qui par ses caractéristiques écologiques favorisait un contact

étroit avec les insectes vecteurs de diverses espèces de Plasmodiums plaide en faveur de la thèse qui fait de l'Afrique le berceau du paludisme des primates.

On a pu établir avec certitude que le paludisme des primates existe depuis très longtemps dans l'Ancien Monde. On croit que cette affection, originaire d'Afrique tropicale, a emprunté la vallée du Nil pour se propager jusqu'aux rives de la Méditerranée d'une part, et d'autre part en Mésopotamie, dans la péninsule indienne et en Chine. Ces trois régions furent les principaux centres à partir desquels le paludisme se répandit sur une grande partie du monde.

Bien que la preuve n'en soit pas encore faite, il est probable que le paludisme existait dans les Amériques avant la conquête espagnole. Les anthropologistes modernes admettent que les tribus primitives entreprenaient de très longs voyages en haute mer, et tout indique que le paludisme a été apporté de l'Orient au Nouveau Monde, longtemps avant Colomb, par des peuples navigateurs.

Des fouilles ont récemment mis au jour dans les Amériques des momies vieilles de milliers d'années. Il n'est pas impossible que les méthodes immunologiques modernes, appliquées à l'examen des restes momifiés des anciens habitants de l'Amérique, révèlent la présence d'anticorps spécifiques ayant résisté à l'épreuve du temps, et apportent la solution de cette énigme qu'est l'histoire des premiers temps du paludisme sur ce continent.

REFERENCES

Abelson, P. H. (1956) *Sci. Amer.*, **195**, 83

Ackerknecht, E. H. (1948) *Cinchona and malaria in pre-eradication America*, New York, Froben Press (Victor Robinson Memorial Volume)

Adler, S. (1933) *Bull. Soc. Path. exot.*, **26**, 207

Adler, S. & Foner, A. (1961) *Israel J. exp. Med.*, **11**, 1

Alimen, H. (1955) *La préhistoire de l'Afrique*, Paris, Boubée

Allison, A. C. (1961) *Genetical variation in human populations*, Oxford, Pergamon

Allison, A. C. (1963) *Inherited factors in blood conferring resistance to protozoa.* In: Garnham, P. C. C., Pierce, A. E. & Roitt, I., ed., *Immunity to protozoa*, Oxford, Blackwell, p. 109

Alvarado, C. A. & Farid, M. A. (1963) *The epidemiology of malaria under the impact of eradication attack.* In: *Seventh International Congresses of Tropical Medicine and Malaria. Abstracts of the papers*, Rio de Janeiro, p. 514

Arcos, G. (1938) *An. Univ. cent. Ecuad.*, **61**, 267

Ashburn, P. M. (1947) *The ranks of death—a medical history of the conquest of America*, New York, Howard McCann

Baer, J. G. (1951) *Ecology of animal parasites*, Urbana, University of Illinois

Ball, G. H. (1943) *Amer. Nat.*, **77**, 345

Ball, G. H. (1960) *J. Protozool.*, **7**, 1

Barbieri, A. (1910) *Sem. méd. (B. Aires)*, **12**, 1368

Bates, M. (1949) *The natural history of mosquitos*, New York, Macmillan

Bates, M. (1962) *The human environment*, Berkeley, University of California (Horace Albright Conservation Lectures)

Beklemišev, V. N. (1956) *Zool. Ž.*, **35**, 1765

Bibby, J. (1962) *The testimony of the spade*, London, Fontana

Boyd, M. F. (1930) *An introduction to malariology*, Cambridge, Mass., Harvard University Press

Boyd, M. F., ed. (1949) *Malariology*, Philadelphia & London, Saunders

Bray, R. S. (1957) *Studies on the exo-erythrocytic cycle of the genus Plasmodium*, London, Lewis

Bray, R. S. (1960) *Amer. J. trop. Med. Hyg.*, **9**, 466

Bray, R. S. (1963a) *Ergebn. Mikrobiol.*, **36**, 169

Bray, R. S. (1963b) *Int. Rev. trop. Med.*, **2**, 41

Bray, R. S. (1963c) *J. Parasit.*, **49**, 888

Bray, R. S. & Garnham, P. C. C. (1964) *Bull. Wld Hlth Org.*, **31**, 143

Bruce-Chwatt, L. J. (1963) *Congenital transmission of immunity in malaria.* In: Garnham, P. C. C., Pierce, A. E. & Roitt, I., ed., *Immunity to protozoa*, Oxford, Blackwell, p. 89

Burnet, M. (1953) *Natural history of infectious disease*, London, Cambridge University Press

Burnet, M. (1964) *Nature (Lond.)*, **203**, 451

Büttner-Janusch, J., ed. (1963) *Evolutionary and genetic biology of primates*, New York & London, Academic Press, vol. 1

Cameron, T. W. M. (1950) *Trans. roy. Soc. Canada*, **44**, 1

Carpenter, F. M. (1953) *Amer. Scient.*, **41**, 256

Carter, H. R. (1931) *Yellow fever : an epidemiological and historical study of its place of origin*, Baltimore, Williams & Wilkins

Cary, M. & Warmington, E. H. (1963) *The ancient explorers*, Harmondsworth, Penguin Books

Caullery, M. (1952) *Parasitism and symbiosis*, London, Sidgwick & Jackson

Celli, A. (1925) *Storia della malaria nell'agro Romano*, Città di Castello, Accademia dei Lincei

Childe, G. (1942) *What happened in history*, Harmondsworth, Penguin Books

Christophers, S. R. (1934) *Proc. roy. Soc.*, **27**, 991

Christophers, S. R. (1960) *Aedes aegypti*, London, Cambridge University Press

Clark, J. D. (1959) *The prehistory of southern Africa*, Harmondsworth, Penguin Books

Clark, W. E. Le G. (1959) *The antecedents of man*, Edinburgh, University Press
Clarke, G. (1961) *World prehistory*, London, Cambridge University Press
Coatney, G. R. (1963a) *J. Amer. med. Ass.*, **184**, 876
Coatney, G. R. (1963b) *J. Parasit.*, **49**, 919
Cockburn, A. T. (1963) *The evolution and eradication of infectious diseases*, Baltimore, Johns Hopkins University Press
Cole, S. (1964) *New Scient.*, **22**, 606
Contacos, P. G. & Coatney, G. R. (1963) *J. Parasit.*, **49**, 912
Corradetti, A. (1963) *Parassitologia*, **5**, 177
Coupland, R. (1933) *The British anti-slavery movement*, London, Butterworth
Deevey, E. S. (1960) *Sci. Amer.*, **203**, 195
Deschamps, H. (1962) *L'Afrique noire pré-coloniale*, Paris, Presses Universitaires de France
Díaz del Castillo, Bernal [1632] *The conquest of new Spain* (J. M. Cohen, trans., 1963), Harmondsworth, Penguin Books
Ebbell, B. (1937) *The papyrus Ebers : the greatest Egyptian medical document*, Copenhagen
Edwards, F. W. (1923) *Quart. J. geolog. Soc.*, **79**, 139
Elton, C. S. (1958) *The ecology of invasions by animals and plants*, New York, Wiley
Eyles, D. E. (1963) *J. Parasit.*, **49**, 866
Flores, F. A. (1886) *Historia de la medicina en México*, México
Garcilaso de la Vega (El Inca) (1723) *Primera parte de los comentarios reales que tratan de el origen de los Incas . . .*, 2nd ed., Madrid (*The first part of the royal commentaries of the Yncas*, by C. R. Markham, trans., 1869-71, London, Hakluyt Society)
Garnham, P. C. C. (1954) *Ann. Rev. Microbiol.*, **8**, 153
Garnham, P. C. C. (1955) *The comparative pathogenicity of protozoa in their vertebrate and invertebrate hosts.* In: Society for General Microbiology, *Mechanisms of microbiol pathogenicity*, Cambridge, University Press, p. 191
Garnham, P. C. C. (1957) *Cyclical transmission of haemosporidia.* In: Smith, H., ed., *Biological aspects of transmission of disease*, London, Oliver & Boyd, p. 101
Garnham, P. C. C. (1963a) *An introduction to protozoal immunity.* In: Garnham, P. C. C., Pierce, A. E. & Roitt, I., ed., *Immunity to protozoa*, Oxford, Blackwell, p. 3
Garnham, P. C. C. (1963b) *J. Parasit.*, **49**, 905
Garnham, P. C. C. (1964) *Factors influencing the development of protozoa in their arthropod hosts :* In: Taylor, A. E. R., ed., *Host-parasite relationships in invertebrate hosts. Second symposium of the British Society for Parasitology*, Oxford, Blackwell, p. 33
Garrison, F. H. (1929) *An introduction to the history of medicine*, Philadelphia & London, Saunders
Ghalioungui, P. (1963) *Magic and medical science in ancient Egypt*, London, Hodder & Stoughton
González Holguín, Diego (1608) *Vocabulario de la lengua general de todo el Perú llamada lengua Quichua, o del Inca*, Ciudad de los Reyes
Guerra, F. (1964) *Med. Hist.*, **8**, 31
Hackett, C. J. (1963) *Bull. Wld Hlth Org.*, **29**, 7
Hackett, L. W. (1949) *Distribution of malaria.* In: Boyd (1949) vol. 1, p. 722
Haggis, A. W. (1941) *Bull. Hist. Med.*, **10**, 417
Harrison, G. A., Weiner, J. S., Tanner, J. M. & Barnicot, N. A. (1964) *Human biology*, London, Oxford University Press
Hegner, R. (1928) *Quart. Rev. Biol.*, **3**, 225
Hernández, Francisco (1615) *Quatro libros de la naturaleza y virtudes medicinales de las plantas y animales de la Nueva España, anotados por Fray Francisco Ximénez*, Mexico (Reprinted in Morelia, 1888)
Hirsch, A. (1883-86) *Handbook of geographical and historical pathology*, London, New Sydenham Society (English translation)
Hoare, C. A. (1948) *The relationship of haemoflagellates.* In: *Proceedings of the Fourth International Congresses of Tropical Medicine and Malaria, Washington, D.C.*, Washington, D.C., Department of State, vol. 2, p. 1110
Hoare, C. A. (1962) *Acta trop. (Basel)*, **19**, 281
Hoeppli, R. (1959) *Parasites and parasitic infections in early medicine and science*, Singapore, University of Malaya
Hoops, A. L. (1934) *Malay. med. J.*, **9**, 123
Howells, W. (1960) *Sci. Amer.*, **203**, 113
Huff, C. G. (1938) *Quart. Rev. Biol.*, **13**, 196
Huff, C. G. (1945) *Rev. Inst. Salubr. Enferm. trop. (Méx.)*, **6**, 253
Huff, C. G. (1958) *Rice Inst. Pamphl.*, **45**, 55
Hui-Lin-Li (1960-61) *Harv. J. Asiat. Stud.*, **23**, 61
Humboldt, A. von (1821) *An account of the cinchona forests of South America*, London
Huxley, J. (1953) *Evolution in action*, London, Chatto & Windus
Ingstad, H. (1964) *Nat. geogr. Mag.*, **126**, 708
Jantsch, M. (1948) *Die Malaria, ein geschichtliches Ueberblick*, Wien, Deuticke
Jaramillo-Arango, J. (1950) *The conquest of malaria*, London, Heinemann
Jarcho, S. (1964) *Bull. Hist. Med.*, **38**, 1
Jeffreys, M. D. W. (1953) *Scientia (Milano)*, **6**, 1
Jennings, J. D. & Norbeck, E., ed. (1964) *Prehistoric man in the new world*, Chicago, University Press
Johnston, H. H. (1937) *The opening up of Africa*, London, Butterworth
Jones, W. H. S. (1909) *Malaria and Greek history*, Manchester, University Press
Jones, W. A. S., Ross, R. & Elliott, G. G. (1907) *Malaria, a neglected factor in the history of Greece and Rome*, Cambridge, University Press
J. Parasit., 1963, **49**, 865-919
Knowles, R. & Senior-White, R. (1930) *Indian med. Res. Mem.*, No. 18
Koch, R. (1898) *Arb. K. GesundhAmt.*, **14**, 292

Lastres, J. B. (1951) *Historia de la medicina peruana*, Lima, Universidad Nacional de San Marcos
Laudonnière, R. (1853) *Histoire notable de la Floride située en Indes Occidentales*, Paris
Leakey, L. S. B. (1961) *The progress and evolution of man in Africa*, London, Oxford University Press
Leakey, L. S. B. & Leakey, M. D. (1963) *Nature (Lond.)*, **202**, 5
Leakey, L. S. B., Tobias, P. U. & Napier, J. R. (1964) *Nature (Lond.)*, **202**, 7
Livadas, G. A. (1959) *Riv. Parassit.*, **20**, 299
Livingstone, F. S. (1961) *Hum. Biol.*, **33**, 205
Macdonald, G. (1957) *The epidemiology of malaria*, London, Oxford University Press
MacGowan, K. & Hester, J. A. (1962) *Early man in the New World*, New York, Doubleday
McNeill, W. M. (1963) *The rise of the west*, Chicago, University Press
Major, R. H. (1954) *A history of medicine*, Oxford, Blackwell
Manwell, R. D. (1955) *Indian J. Malar.*, **9**, 247
Manwell, R. D. (1961) *Introduction to protozoology*, London, Arnold
Markham, C. R. (1880) *Peruvian bark*, London, Murray
Markham, U. (1908) *Vocabularies of the general language of the Incas of Peru*, London, Williams & Norgate
Martini, E. (1930) *Culicidae*. In: Lindner, F., ed., *Die Fliegen der Palaearktischen Region*, Stuttgart
Mason, J. A. (1961) *The ancient civilizations of Peru*, Harmondsworth, Penguin Books
Mattingly, P. F. (1960) *Trans. roy. Soc. trop. Med.*, **54**, 97
Mattingly, P. F. (1965) *New Scientist*, **26**, 22
May, J. (1958) *The ecology of human disease*, New York, MD Publications
May, J. (1961) *Studies in disease ecology*, New York, Hafner
Mayr, E. (1957) *Evolutionary aspects of host specificity among parasites of vertebrates*. In: Mayr, E. & Baer, J., ed., *Premier Symposium sur la Spécificité parasitaire des Parasites des Vertébrés*, Neuchâtel, Institut de Zoologie
Mečnikov, I. I. (1887) *Russ. Med.*, **12**, 207
Meillon, B. de (1947) *Ethiopian Anophelini*, Johannesburg, South African Institute for Medical Research
Mesnil, F. (1899) *Essai sur la classification et l'origine des sporozoaires*. In: *Cinquantenaire de la Société de Biologie*, Paris, p. 258 (jubilee volume)
Missiroli, A. (1934) *Lezioni sulla epidemiologia e profilassi della malaria*, Roma, Courrier
Molina, Alonso de (1571) *Vocabulario de la lengua mexicana* (Facsimile ed., Leipzig, 1880)
Moodie, R. L. (1923) *The antiquity of disease*, Chicago, University Press
Morison, S. E. (1924) *Admiral of the ocean sea : a life of Christopher Colombus*, Boston, Little Brown
Moškovskij, Š. D. (1948) *Tr. Akad. med. Nauk S.S.S.R.*, No. 1, p. 155
Moškovskij, Š. D. (1954) [*Concepts and aims of functional parasitology*], In: [*Third ecological conference*], Kiev, State University
Motulsky, A. G. (1960) *Hum. Biol.*, **32**, 28
Motulsky, A. G. (1964) *Amer. J. trop. Med. Hyg.*, **13**, 147
Moulder, J. W. (1962) *Biochemistry of intracellular parasitism*, Chicago, University Press
Muller, R. F. G. (1937) *Artibus Asiae*, **6**, 230
Napier, J. (1964) *Discovery*, **25**, 32
Netolitsky, F. (1932) *Wien med. Wschr.*, **82**, 229
Nicolle, C. (1933) *Destin des maladies infectieuses*, Paris, Alcan
Noble, E. R. & Noble, G. A. (1964) *Parasitology*, Philadelphia, Lea & Febiger
Oliver, R. & Fage, J. D. (1962) *A short history of Africa*, Harmondsworth, Penguin Books
Oviedo y Valdés, Gonzalo Fernández de, *Historia general y natural de las Indias, islas y tierra-firme del mar océano*. (1851 ed., Madrid)
Pales, L. (1930) *Paléopathologie et pathologie comparative*, Paris, Masson
Pavlovskij, E. N. (1946-48) [*Textbook of human parasitology*], Moscow, Academy of Sciences of the USSR
Paz Soldán, C. E. (1938) *Las tercianas del Conde de Chinchon*, Lima, Reforma Medica
Pendle, G. (1963) *History of Latin America*, Harmondsworth, Penguin Books
Penna, J. & Barbieri, A. (1916) *El paludismo*, Buenos Aires
Pfeiffer, R. (1892) *Beiträge zur Protozoerforschung. I. Die Coccidienkrankheiten der Kaninchen*, Berlin
Poma de Ayala, Felipe Guzmán (1587) *Nueva corónica y buen gobierno* (Institut d'Ethnologie, Travaux et Mémoires, vol. 23, Paris, 1936)
Prescott, W. H. (1847) *History of the conquest of Peru*
Preuss, J. (1911) *Biblisch Talmudische Medizin*, Berlin
Raina, B. L. (1951) *Introduction to malaria problem in India*, Bombay
Reichenow, E. (1912) *Die Haemogregarinen*, In: Prowazek, S. J. M., ed., *Handbuch der pathogenen Mikroorganismen*, Leipzig, vol. 2, p. 602
Reid, J. A. & Knight, K. L. (1961) *Ann. trop. Med. Parasit.*, **55**, 474
Reko, V. A. (1931) *Ärztl. Rdsch.*, **41**, 151
Rogers, W. P. (1962) *The nature of parasitism*, New York & London, Academic Press
Ross, H. M. (1964) *Mosquito News*, **24**, 103
Ross, R. (1911) *The prevention of malaria*, London, Murray
Ruffer, A. (1921) *Studies on palaeopathology of Egypt*, Chicago
Russell, P. F. (1955) *Man's mastery of malaria*, London, Oxford University Press
Russell, P. F., West, L. S., Manwell, R. J. & Macdonald, T. (1963) *Practical malariology*, London, Oxford University Press

Sahagún, Fray Bernardino de (1573) *Historia general de las cosas de Nueva España* (Mexico, Bustamente, 1829-30)

Sandosham, A. A. (1960) *The evolution of parasites.* In: *Proceedings of the Centennial Darwin-Wallace and Bicentennial Linnaeus Congress*, Singapore, University of Malaya, vol. 1, p. 95

Sarton, G. (1959) *A history of science*, Cambridge, Mass., Harvard University Press

Schaudinn, F. (1899) *S.-B. Ges. Naturf. Fr. Berl.*, p. 159

Scott, H. H. (1939) *A history of tropical medicine*, London, Arnold

Sergent, E. (1963) *Latent infection and premunition.* In: Garnham, P. C. C., Pierce, A. E. & Roitt, I., ed., *Immunity to protozoa*, Oxford, Blackwell, p. 39

Sharp, A. (1957) *Ancient voyagers in the Pacific*, Harmondsworth, Penguin Books

Sherrington, C. (1940) *Man on his nature*, Harmondsworth, Penguin Books

Short, A. R. (1953) *The Bible and modern medicine*, London, Paternoster

Sigerist, H. E. (1945) *Civilization and disease*, Ithaca, N.Y., Cornell University Press

Sigerist, H. E. (1951) *A history of medicine. Primitive and archaic medicine*, New York, Oxford University Press, vol. 1

Sigerist, H. E. (1960) *Problems of historical-geographical pathology.* In: Roemer, M. I., ed., *Henry E. Sigerist on the sociology of medicine*, New York, MD Publications, p. 299

Simmons, J. S. (1939) *Malaria in Panama*, Baltimore, Johns Hopkins University Press

Simons, E. L. (1963) *A critical re-appraisal of tertiary primates.* In: Büttner-Janusch (1963) p. 66

Simpson, G. G. (1962) *Ann. N.Y. Acad. Sci.*, **102**, 282

Singer, C. & Underwood, H. A. (1962) *A short history of medicine*, Oxford, Clarendon Press

Smith, G. E. & Wood-Jones, F. (1910) *Report on human remains.* In: *Archaeological survey of Nubia. Report for 1907-1908*, Cairo, Ministry of Finance, vol. 2

Smith, M. (1960) *Science*, **131**, 699

Smith, T. (1934) *Parasitism and disease*, Princeton, University Press

Soustelle, J. (1955) *La vie quotidienne des Aztèques à la veille de la conquête*, Paris, Hachette (English trans.: *The daily life of the Aztecs*, Harmondsworth, Penguin Books, 1964)

Sprent, J. F. A. (1962) *Parasitism, immunity and evolution.* In: Leeper, J. N., ed., *The evolution of living organisms*, Melbourne, University Press, p. 149

Springer, G. F. & Williamson, P. (1960) *Science*, **131**, 1858

Stephens, J. W. & Christophers, S. R. (1900) *Rep. Malar. Com. roy. Soc.*, Series 3, p. 4

Stone, A., Knight, K. L. & Starcke, M. (1959) *A synoptic catalog of the mosquitoes of the world*, Washington, D.C., Entomological Society of America

Taliaferro, W. H. (1963) *Cellular and humoral factors in immunity to protozoa.* In: Garnham, P. C. C., Pierce, A. E. & Roitt, I., ed., *Immunity to protozoa*, Oxford, Blackwell, p. 22

Ulloa, J. J. & Ulloa, A. de (1748) *Relación histórica del viáge hecho de Orden de S. Mag. a la América meridional*, Madrid

Vaillant, G. C. (1961) *The Aztecs of Mexico*, Harmondsworth, Penguin Books

Vaughan, C. V. (1923) *Epidemiology and public health*, St Louis

Ward, R. A. (1963) *Exp. Parasit.*, **13**, 328

Warren, M. & Wharton, R. H. (1963) *J. Parasit.*, **49**, 892

Weiss, M. G. & Giusti, D. L. de (1964) *Nature (Lond.)*, **201**, 731

Wellcome, H. S. (1930) *Cinchona tercentenary celebration and exhibition*, London, Wellcome Foundation

Wells, C. (1964) *Bones, bodies and disease*, London, Thames & Hudson

Wenyon, C. M. (1926) *Protozoology*, London, Baillière, Tindall & Cox

Zeuner, F. R. (1950) *Dating the past*, London, Methuen