9. MALARIA

Malaria remains the most frequently encountered health problem in the tropics. From the start of the colonial era, it sparked great interest; but then diagnosis became routine, transmission pathways were elucidated, and treatment and prevention became standardized so that fascination waned.

Despite the extraordinary magnitude of the problem, the authorities never gave it priority and, as a consequence, malaria research conducted by a few enthusiastic malariologists, was never more than fragmentary. A few exceptions, however, should be mentioned, for example whenever epidemics broke out in non-immune populations who were suddenly exposed to the risk of infection, as occurred when workers from the malaria-free high plateaux were recruited to work on alluvial mining sites, and the increased number of breeding places gave rise to intense disease transmission. The same problem affected the local populations of high-altitude areas when they shifted to farming the more fertile land in valleys, lowlands and other low-lying areas.

In 1950-51 the Commission du Paludisme du Conseil Supérieur de l’Hygiène Coloniale (Malaria Committee of the Higher Council of Colonial Hygiene) tried to determine the importance of malaria as a cause of mortality, basing its study on statistical records and various other observations. However the parameters varied too widely to allow for indisputable conclusions. According to one rough estimate, general mortality due to malaria was 3 to 5%. In infants up to one year of age it rose as high as 30 to 40%, during the second year of life to 10-15 %, and reached in the three-to-six-years of age 6-10%. Malaria thus appeared to be the major cause of mortality, especially in early childhood.

The introduction of residual insecticides and slow-acting antimalarial drugs offered new weapons against the disease. But because of the prevailing highly complex epidemiological situation, tropical Africa was excluded from the World Health Organization’s global eradication programme. This led the medical authorities of the Congo (Zaire) to work out their own strategy based on adapted anopheles control campaigns and chemoprophylaxis, the latter being directed mainly at infants and young children.

The creation of a (vertical) autonomous service, not under control of the Medical Department, was ruled out; however the need to train malarial hygienists eligible for WHO’s training programmes was strongly emphasized. Judicious use of the available means could not eradicate either vectors or parasites, but did nonetheless considerably reduce the incidence of the disease.

The events of independence have cut this programme short before its effects could be felt throughout the territory. Moreover, the mosquitoes and plasmodia gradually developed resistance to the insecticides and antimalarial drugs in use.

Meanwhile, recent advances in knowledge and techniques have made it possible to launch urban, suburban, and rural pilot programmes straight away, pending the introduction of more general antimalarial measures.

In the interim, health education efforts and the implementation of simple measures compatible with primary health care programmes have also prepared the ground for successful campaigns on a much larger scale.
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A. MALARIA PARASITES AND THE DISEASE
HISTORICAL BACKGROUND

1. Before 1880: the first observations

Known since antiquity, malaria is undoubtedly one of the diseases to have caused the highest number of victims throughout the ages, and worldwide.

Up until the nineteenth century, fevers (which were often fatal) were the major hindrance to exploration of the African interior. Explorers, soldiers, missionaries and traders all cited fevers in their accounts as the cause of their failures and of the massive losses their activities entailed. *Falciparum* malaria was definitely the chief cause of these fevers and deaths.

Differentiating between the tangle of fevers to cure ("opprobria medicorum", as stated by Sydenham) was no easy task. Some fevers were identified by their frequency or the appearance of conclusive symptoms, others were linked to a typical ecology, and still others would be recognized by their responsiveness to certain drugs. By this last alternative the first stage to recognize malaria should be reached.

In the seventeenth century Don Juan Lopez de Canizares (1630), the Jesuit father Barnabe de Cobo (1632), and the Augustinian monk, Antonio de la Calencha (1632), reported that intermittent fevers could be treated with quinquina bark powder. This powder, which originated in the Peruvian Andes, was made from the bark of the Cinchona. It was variously known as the Countess’s powder, the Jesuits’ powder, and the Cardinal’s powder. The astute Talbort (1682) displayed it to public as a mysterious English remedy, thereby increasing the demand and the price, and he lined his pockets very nicely! These powders all became part of medical folkloric mythology. La Fontaine even wrote a Poem on Quinquina (1682).

Advances in chemistry starting in the eighteenth century prompted many pharmacists, biologists, and doctors to try to isolate the active ingredient in quinquina bark powder. The Portuguese physician Gomez went further when in 1810, he isolated a crystalline substance that he called cinchonine. However, the Parisian pharmacists Pelletier and Caventou were the ones who actually isolated quinine in 1820 and showed how the various salts of this alkaloid could be produced. The use of quinine salts for curative treatment was perfected only very gradually, through trial and error. Chomel (1821) was the first one to conduct clinical tests with quinine sulphate and cinchonine sulphate, both produced by Pelletier.

Amazingly, *malaria* and *paludisme*, the medical terms in common use today in English- and French-speaking countries respectively appeared very late in medical literature.

a) Malaria, meaning foul air, had been used since the Middle Ages and was common in Italy; and even later, Horace Walpole (1740), Shelley (1818), and Byron (1821) used it in the accounts of their travels.

The first doctor to use the English term *malaria* in his writings was MacCullough in 1828.

b) The term *paludisme* in French comes from the Latin *palus* (= marshy, malarial) and has paludism, paludous, palustral as English counterparts. *Palud, palude,* and *palus* were definitely used as early as 1564 to define alluvial soil and the soil of ancient littoral marshes. The connection between these areas’ effluvia and miasmata and periodic fevers gave rise in French to the word *impaludisme*, currently used between 1846 and 1908, but replaced soon by *paludisme*.

Jacquot was the first to use the term *paludisme* in the French medical literature in 1857.

These appellations have given way to *malaria* and its derived forms, leaving the root *palus* to refer primarily to marshes.

2. The period from 1880 to 1900

Advances in medical knowledge are never the work of one individual. It is by learning from their predecessors that some investigators could see new light arising from accumulated observations. Several famous research-workers’ names mark the stages of progress.

A. Laveran is one such exceptional individual. The presence of a brown pigment in the erythrocytes of some febrile patients had been known for years (Meckel, 1847; Rasori, 1846; Virchov, 1853), but its significance remained obscure. It was while assiduously using the microscope to examine fresh blood smears from febrile patients that Laveran lighted upon an exflagellation, the significance of which he grasped immediately. As the waving filaments could not be ramifications of the red blood cells, they were perfecive indicators of the presence of a living parasite, of which the pigment was a component. The blood stage of the malaria parasite had thus been detected. It
would however not be recognized as the pathogen of the disease until it had run the usual gauntlet of objections and disputes.

Manson is another example of an investigator pursuing an idea. Prompted by the example of the transmission of Bancroftian filariasis by nocturnal mosquitoes (C. fatigans), in the dissected tissues of which he had found the filarial embryos, he hypothesized that a similar pathway might be involved in the transmission of malaria. No disrespect is meant in pointing out his mistake in that, influenced by Steensstrup's observations of parasite development in molluscs, Manson believed that man was infected by drinking water into which the filarial embryos had been released when the mosquitoes died.

Still, his chief merit was to have appreciated Ross's abilities and given him the motivation to undertake research on the mosquito-borne transmission of malaria. This hypothesis was not entirely new: it had earlier been brought forward by Crawford (1807), Nott (1848), Beauperthuy (1854), Laveran (1884), and Pfeiffer (1892).

In India Ross did the initial spadework admirably. He found the first stages of transformation of the malaria parasite in the midguts of spotted-wing mosquitoes that had stung parasite-bearing humans. At this very encouraging stage of his research he was transferred to a non-malarious area. He did not let this stop him and resumed his investigations on sparrows carrying plasmodia. He worked out the complete parasite life cycle in the Culicids.

This modest investigator, endowed with unshakable faith, solved an equation with two unknowns, namely, the vector and the site in the vector harbouring the parasite. He showed that transmission from person to person or from bird to bird occurred via a mosquito sting. Aware of the unveiled prospects, as a marvelous lesson for research-workers he wrote: "The door is unlocked, I have crossed the threshold, and now I am reaping treasures."

The contribution of Italian malariologists is of utmost importance. By comparing maps representing the distribution of anophelines with others showing the malaria foci, they were able to foretell that anophelines were the likely carriers of the disease. They were able moreover to transmit the disease to volunteers exposed to stings by infected mosquitoes in the countryside of Rome.

Once the pathogen had been identified and the use of the active alkaloid had become possible, Laveran was able to assert that quinquina was "the truly specific remedy to oppose to malaria".

The therapeutic doses were gradually defined at different occasions, during military operations, by navy doctors visiting ports in the tropics, or during explorers' travels and scientific expeditions, and by the first generation of specialists in tropical medicine or missionaries.

At first the doses were tailored to the individual, taking into account his weight and forceful or faint hearted character. With doses ranging from 10 cgt to 1 g or more the results could only be extremely variable. What is more, no distinction was made at that time between primary attack and relapses in cases of chronic carriers. Quinine was championed by some, contested by others.

The first trial of preventive administration of quinine seems to have been conducted by Bourvenal (1717) during the siege of Belgrade. He was reputed to have put an end to a spate of pernicious attacks and deaths, but this was actually an example of early treatment rather than true prophylaxis. Later on the dose depended on the type of cure: if the risk of malaria was serious but limited in time, curative doses were given, otherwise, sub-curative doses were used.

Of course, agreement on the dosage levels and frequency of administration could not be expected from the outset. Moreover, attention was drawn from the start to the existence of strains that were resistant to quinine, thus proving in effect that there were variations in sensitivity, the Mediterranean strains of P. falciparum being two times less sensitive to quinine than the tropical African strains, effective doses being 2 g for the former and 1 g for the latter.

Discussion about curative doses were centered on whether single or divided doses should be used.

Laveran recommended intermittent doses in intermediary amounts. Unanimity on the route of administration (per os, IM, or IV) was never reached. On the other hand, there was tacit agreement that IV administration should be limited to algid malaria cases and that quinine should be taken by mouth whenever possible. Nevertheless, some proponents of IV injections remained unmoved, despite the unnecessary risks that such a procedure entailed. The duration of treatment and number of courses to be administered were the objects of innumerable discussions.

The same questions came up for prophylaxis. Should the quinine be administered daily, twice a week (two days on and three days off), or weekly, and what should be the amount? Some examples were 5 cgt every three days (Koch), 1 g every four days (Ziemann), 30 to 50 cgt daily for some, or 10 to 20 cgt daily for others. The Italians recommended 40 cgt per day and twice this dose in heavily infested areas.
MALARIA

The problem was to strike a balance between efficacy and undesirable side effects. In addition, prevention had to be regular; a daily, almost automatic, small dose was a good guarantee against disease. It would have been logical to recommend higher doses in the first months of a stay in a malarious region because quinine controls parasitaemia more easily when sustained by the subject’s personal resistance, which develops only after prolonged exposure.

Once the synthetic antimalarials had increased the pharmacological arsenal, the efficacy of the various therapeutic and prophylactic processes were determined by assaying the levels of the drugs, including quinine, in the blood.

3. Observations and studies in the Congo (Zaire)

The first studies of malaria in the Congo Free State followed shortly after the discovery of the vector, which destroyed once and for all the old theories of mists, miasmata, and other effluvia from ground, water, or decomposing organic matter. Research carried out between 1899 and 1900 by Van Campenhout and Dryepondt (1901) at the Leopoldville Medical Laboratory led the investigators to declare that malaria ranked first among the diseases affecting Europeans in the Congo. Van Campenhout and Dryepondt also showed that the so-called acclimatization or climatic fevers generally attributed to meteorological factors, were actually attacks of malaria, as proven by the presence of plasmodia in the blood. The same study attributed 88% of the malarial fevers to the agency of malignant tertian malaria, 10% to the agency of benign tertian malaria, and 2% to the action of quartan malaria.

The malarial attacks were treated with multiple 50 ctcg doses of quinine.

Prevention focused on eradicating the anopheles larvae by draining marshes or spreading chemical larvicides and on protecting people from the bites of the adult mosquitoes by material means (mosquito netting). Chemoprophylaxis with quinine was advised, but the doses (1 g once a week) were too low to be effective. Many Europeans, particularly religious missionaries, took a tip of a knife of quinine powder.

Blackwater fever (see p. 1493) was clearly a consequence of chronic malaria added to other ailments such as cold, fatigue, physical or mental stress, and quinine abuse.

Broden (1906), who followed Van Campenhout as head of the Leopoldville Medical laboratory, continued the work on blackwater fever between 1901 and 1905. He confirmed that it was a complication of malaria and was averted by malaria prevention.

These first publications were followed by studies of all aspects of malaria, such as malaria indices, the species distribution of anopheles mosquitoes, epidemiology, prevalence, transmission, clinical and parasitological diagnosis (aided much later by the development of serological techniques), treatment, prevention, and also the administrative and technical measures to break the transmission chain. The Annales de la Société belge de Médecine Tropicale contained 331 reports dealing with malaria between 1920 and 1969.

Malaria was omnipresent in Zaire, Rwanda, and Burundi except at high-altitude areas. No one was safe from plasmodia, for the inhabitants of malaria-free areas ran an even greater risk of infection if they travelled to infested areas.

In most of the infested areas transmission did not vary over the year, leading the population to a state of equilibrium or tolerance to the parasite. The price to pay for reaching this balance in the so-called holoendemic areas was high morbidity, and a fair degree of mortality among suckling infants, once they were no longer protected by the resistance transmitted through their mothers. Attacks of malaria only occurred when various incidents would upset this balance.

In areas of seasonal transmission pattern, more fluctuations in the balance increased the number of clinical cases at the moment a rise in vector population gave new impetus to the transmission chain.

In malaria-free areas, the introduction of vectors, as a result of faulty drainage of lowlands to increase farm acreage, could set off veritable but short malaria outbreaks.

Secondly, most studies focussed logically on sporadic outbreaks of this kind. Summarizing these observations is not easy. Two authors – A. Duren (1937, 1953) and J. Gillet (1953) – nevertheless tried to give a comprehensive overview of the situation. In addition, two committees of the Conseil supérieur d’Hygiène coloniale (Higher Board of Colonial Hygiene) reported in 1951 on malaria chemoprophylaxis and the coordination of malaria control measures (Rodhain, 1951).

These studies were based on the malaria morbidity and mortality statistics recorded in hospitals and dispensaries, and also on various surveys on parasite and spleen rates in a certain number of communities.

The morbidity figures were no more than rough guidelines as they were relying on highly questionable statistics. The native population paid little attention to attacks of fever, considered as an inevitable misfor-
tune of life, and was not motivated to seek medical advice, especially if the health centre or post was not nearby. Others learned to rely on self-medication. Finally, the statistics were representative only for people living close to a health centre or for the apprehensive (who would hence seek advice and treatment).

a) For the Europeans, for whom the statistics had a chance of being more accurate, Duren calculated an annual morbidity for malaria and blackwater fever of 220 per 1,000 population between 1918 and 1920, 152 per 1,000 between 1921 and 1930, and 141 per 1,000 for 1931-1934, with case-fatality rates of 2.9%, 2%, and 1.3%, respectively.

The general mortality rate and the specific mortality due to malaria among the Europeans over comparable periods were as follows:
- annual mortality rate, all causes included, between 1909 and 1920 of 28.17 per 1,000, with specific mortality due to malaria of 6.39 per 1,000, or 22.7% of all deaths;
- between 1921 and 1930, the rates were respectively 13.27 per 1,000 and for malaria 3.1 per 1,000, or 22.6% of all deaths;
- for 1931 to 1935 the rates dropped respectively to 9.58 per 1,000 and 1.89 per 1,000, or 19.7% of all deaths due to malaria.

For the entire period preceding the advent of the major synthetic antimalarials, the disease thus accounted for roughly 20% of deaths among non-Africans.

Most of the deaths were due to cerebral malaria which is the most severe complication of *P. falciparum* malaria. Erythrocytes in which schizonts are developing are trapped in the capillaries of the internal organs, where the schizogony occurs rather than in peripheral capillaries. The infected erythrocytes produce acute circulation impairment which in the brain induces coma and rapid death. The sequestration of erythrocytes is probably due to immunologic mechanisms producing cytokins and particularly TNF (Tumour Necrosis factor).

b) Among the local population, except in occasional epidemics, the majority of malaria victims were infants and young children. Most of the deaths in these categories did not occur in hospitals. The situation had to be assessed by turning to other data, especially those from child welfare clinics and from charitable institutions for children. *Platel* and *Vandergoten* (1945) and *Kivits* (1951) looked into these settings.

Duren (1951) had concluded from the existing studies that malaria killed 14 to 22 per 1,000 children aged 0 to 3 years, the averages being 32 per 1,000 in the first year of life, 12 per 1,000 in the second, and 8.5 per thousand in the third year of life. These figures referred to a selected population of children; indeed it were those who had been checked regularly since birth, often received at least partial chemoprophylaxis, and were treated at the first signs of illness. The death rates in remote areas lacking surveillance were definitively much higher.

*Janssens,* going further (1952), tried to produce objective figures through a series of post-mortems performed in a closely-monitored mining population. Choosing among the various factors of fatality involved, after studying the clinical, macroscopic, and histopathological findings and weighing the facts in the light of the specific ecological conditions prevailing at the time, he determined that malaria accounted for 12.3% of the deaths in the series.

Surveys based on parasite and spleen indices (see p. 1454) were conducted in various communities. These combined indices often yielded infection rates of more than 50% in the 0 to 15 years age group. Moreover, sustained follow-up of children over the first three years of life showed that few of them escaped infection.

All four human plasmodium species were found in the Congo. *P. falciparum* predominated (about 85% of the total), with *P. malariae* a distant second (12%), followed by *P. vivax* (1.7%) and *P. ovale*, encountered even more rarely.

The vectors were, in order of decreasing frequency, *An. gambiae, An. funestus, An. moucheti,* and *An. nili.* Gillet noted that only these four species among the 39 species and 12 varieties of anopheles discovered in the Congo were human malaria vectors. *Rahm* and *Vermylen* (1966) mapped the distribution of anopheles mosquitoes in Zaire, but these data should be updated, especially for the subspecies of the *An. gambiae* complex.

4. Experimental studies on Plasmodia

This analysis has been paralleled by malaria studies in primates, Chiroptera, and rodents.

It were the trials to maintain different strains of plasmodia and vectors for malarial treatment as it was used at that time, which allowed to study malaria of monkeys.

These studies resulted on basis of cross-reactions, in ascertaining that *P. rodhaini* of the chimpanzee and *P. malariae* of men were the same parasite.

Although the problem of malaria and the consequences of the disease for mankind were very well
known before 1940, World War II reminded some powerful Western countries that the problem was not just an inconvenience in some distant tropical areas. The search for new drugs and fundamental research became priorities in many Scientific Institutes. Yet scientists were not very happy about the tools at their disposal, for avian malaria was quite different from the human disease and, even today, primate malaria is not a realistic model for the necessary large-scale research.

Then came 1948, the annus mirabilis, as L.J. Bruce-Chwatt called it. Shortt, Garnham, Covell and Shute described pre-erythrocytic forms of Plasmodium vivax in the human liver and, in doing so, completed our knowledge of the cycle of human malaria. Vincke and M. Lips (1948) discovered a plasmodium in a wild rodent: it was an important milestone in malaria research. It is worthwhile recalling that this breakthrough was the result of relentless search for the origin of the sporozoites found in 7-12% of a wild anophelines, An. darenii, var. millecampsi, from December to February. These mosquitoes were caught in the forest corridors of Kisanga and Kasapa, vestiges of the primeval tropical forest located a few kilometres from Lubumbashi. The host was finally identified: two types of Thamnomys surdaster out of the 358 tree-dwelling rodents examined were found to have slight parasitaemia.

The significance of this discovery as a powerful research tool soon became evident. Plasmodium berghei, named after L. van den Berghe, the Director of the Institute for Scientific Research in Central Africa (IRASAC), presented many of the characteristics of the human pathogen and offered an almost ideal model for systematic research.

When Vincke finally succeeded with scientific stubbornness and thorough knowledge of nature in isolating the new plasmodium he did not realize at once what an epoch-making discovery he had made.

Moreover, the parasites proved inoculable in common laboratory animals, opening a whole new avenue of research leading to advances in parasitology, immunology, physio-pathological mechanisms of the disease and in targeted medication. For this discovery I. Vincke was awarded the Chagas medal, of which only one has ever been struck.

In 1964 the Institute of Tropical Medicine held an important international colloquium on P. berghei to take stock of the advancement of knowledge in this field. The bibliography compiled by then contained more than 500 titles concerning studies of Plasmodium berghei infections produced in various rodents and its transmission by various Anopheles mosquitoes, while hundreds more would follow, such as P. yoelii.

Using A. stephensi, Yoeli and his coworkers were able to describe the primary exo-erythrocytic schizonts in the liver of Thamnomys, hamsters, young albino rats and mice (Yoeli and Most, 1965).

The regular cyclical transmission of P. berghei berghei had finally become possible and light was thrown on every stage of the parasite's life cycle.

5. Malaria control after World War II

The methodology of malaria control varied in course of time, and in line with available means. The initial phase, which focused on reducing or avoiding man-vector contact did not end until the powerful residual insecticides came on the scene, by the end of World War II. Work focused then on the vectors, on basis of ecological, geographic, and taxonomic studies.

Modern identification methods allowed the different species complexes to be subdivided into subgroups involved in the transmission of human malaria to a varying degree so as to provide the key to some, until then, incomprehensible observations. One practical but extremely important remark was that the control of non-vector species (which are annoying because of their bites) should not be neglected, for their disappearance would prove to the public the success of the mosquito control measures. However, for maliariologists and biologists, eradicating the Anopheles remained the basic goal.

Today physical means to avoid mosquito contact - bed nets, metal or nylon screens on windows, grillwork drums at outer doors - remain very useful. They have become even more interesting since the discovery that larger meshes can be used if they are soaked in insecticides or insect repellents. Such compounds, especially the pyrethroids, should not be overlooked.

The aims of the ecological control methods are to eradicate or to make unusable by the mosquito the breeding grounds in which he dwells. Filling in ponds, draining swamps, removing rainwater and sewage, changing the flow of the watercourses, clearing the river banks of weeds, etc., are all possibilities. However such techniques can be a double-edged sword, as badly executed draining can actually increase the number of breeding grounds.

Larvae can also be controlled by applying chemicals such as petrol, Paris green, and synthetic insecticides to breeding grounds. As recommended above one should avoid the development of various Culicids by eliminating all containers that are potential sites for culex but not for anopheles larvae. This concern cov-
ers also the objectives of environmental sanitation and helps to win the public’s confidence, a prerequisite for public participation.

Attempts to control the adult mosquitoes involved the use of pyrethrum powder or extract, especially in the workers’ camps, but yielded fairly uneven results.

Last but not least came individual chemoprophyaxis with quinine or mepacrine. For infants and young children chemoprophyaxis with quinine drops, solutions or tablets, as part of maternal and child health activities could not have yielded tangible results, given the drug’s rapid clearance rate, the large intervals between dose administrations, and irregular attendance. Combining quinine with plasmochin in order to reduce transmission through the latter’s action on the gametocytes rarely had any advantage, and increased the risk of side effects. It was ill-suited for mass treatment schemes.

In contrast, the correct prophylaxis with quinine for recruits (either military or workers) and their families coming from malaria-free or from only slightly affected areas saved many lives and reduced malarial morbidity during the so-called acclimatization period.

The scarcity of quinine during the Second World War resulted in the more frequent recourse to mepacrine (Atebrine®). Its therapeutic and prophylactic performance was comparable to that of quinine, but complicated by more undesirable side effects such as yellow colouring of the skin, minor mood disorders.

The aftermath of the war was marked by the introduction of both newer synthetic antimalarials with slower clearance rates than quinine (chloroquine, proguanil, pyrimethamine) and of residual contact insecticides (DDT, HCH, dieldrin).

These substances radically changed the face of malaria control. Effective chemoprophyaxis became possible through weekly or even fortnightly medication provided in child welfare clinics and schools, while insects could be eradicated from whole settlements by house-spraying of contact insecticides at variable intervals (3 to 6 months).

DDT spraying campaigns were conducted starting in 1947 in various towns, Elisabethville (Lubumbashi), Albertville (Moba), and Astrida (Butare, Rwanda: Jadin and assistants, 1951) workers’ camps (Ituri, Maniema), and various rural areas, (Rwanda-Urundi: Lambrecht, 1954).

The anophelines mosquitoes were eradicated fairly quickly from Elisabethville and within a radius of 30 kilometres from the city; this accounted for a remarkable drop in the parasite indices. The effect in other areas was less pronounced, although noticeable.

6. Recent investigations

Studies of malaria, especially epidemiological and drug-resistance studies, have been conducted recently in Zaire and neighbouring states.

a) In Kinshasa, Ngimbi et al. (1982) have reported a prevalence rate of 33% in children 0 to 15 years old. Seasonal variations are very slight, but social and economic conditions, which vary considerably from one town to the next, influence strongly the prevalence.

Protective immunity slow to develop, as seen by the fact that the parasite rates do not fall significantly in the age group 10 to 15 years, while the percentage antibody carriers in this group shows practically no increase.

b) Taylor working for the EPI (Expanded programme for immunization), also at Kinshasa, conducting research in episodes of fever in children 0 to four years, found an annual incidence of 9.7% in 1983 (Health for All Project, Kinshasa, 1985).

c) Delacollette, working at Katana Hospital in Kivu, at an altitude of 1,500 m above sea level, has also taken interest in malaria. His paludometric studies (1982–1984) indicate that the Katana rural health zone is a stable meso-endemic malarious area. The general parasite rate varies from village to village and in the course of the year from 15 to 50%.

The presumptive chemotherapy for malaria given today in the area is chloroquine, 25 mg per kg, over three days. This treatment is usually prescribed by the nurse in charge of the health centre, based on clinical evidence alone. Roughly 40% of the patients presenting themselves at the health centres are treated for malaria, basically with chloroquine.

However, malaria’s real share in the general morbidity and mortality in the Katana health zone is not known. The antimalarial drugs made available to the population (90% chloroquine, 10% quinine) are distributed only from the health centres, each of which serves some 10,000 people living in a ten to fifteen km radius. In this area chloroquine resistance, especially to P. falciparum, is increasing.

d) Delacollette recently (1987) conducted another study, with the help of the WHO special programmes, with the following aims:
   - to assess general and specific mortality and morbidity and particularly the specific figures due to malaria among the population of a meso-endemic area 1,500 m above sea level;
   - to evaluate the respective influence of the existing health centres and the local volunteers who provide to
the malaria patients the proper treatment by the available chloroquine and quinine in each village;
- to include surveillance of a developing chloroquine resistance into primary health care.

e) A study in Burundi, carried out by Coosemans as part of the Ministry of Health’s Communicable Disease Centre Project and with the help of WHO’s Special Programme performed a detailed horizontal investigation in seven localities of the Rusizi Plain (Coosemans et al., 1984). It was followed by longitudinal studies to pinpoint the endemic pattern in two chosen locations (Coosemans, 1985). This study has led directly to a control programme which could definitely help in reducing the transmission of malaria. The author found that the disease differed greatly from one area to the next along the plain. The longitudinal studies, which included entomological, parasitological, clinical (spleen) and serological parameters, revealed a clear seasonal pattern. The prevalence of malaria is the lowest at the middle of the rainy season and is the highest at the start of the dry season.

In addition, the study showed that the vector potential of *An. arabiensis*, the main and only important malaria vector in this area, was 150 times greater in rice-growing than in cotton-farming areas. As a direct result, a control strategy combining insecticides and various sanitation measures was currently being planned.

f) In 1985 an EEC-funded survey was started in Kinshasa by the Parasitology Department Faculty of Medicine (Professor P.M. Mutumba), in collaboration with EPI of WHO and the Antwerp Institute of Tropical Medicine. Its goals were at one hand to determine in the town of Kinshasa the therapeutic approach taken by the population to attacks of fever in children, and at the other hand to ascertain the part played by malaria in the onset of fever and to detect the mechanism of chloroquine-induced pruritus, and to define the incidence and prevalence of malaria in a few parts of the city.

g) Concerning *P. falciparum*’s resistance to chloroquine, Coosemans, in Burundi, reports 39% failures for *in vivo* chloroquine tests (see p. 1461) on Day 7, and 5% failures for amodiaquin, but less than 2% failures for the sulfadoxine/pyrimethamine combination. The *in vitro* tests revealed that 82% of the isolates were resistant to chloroquine and 86% to pyrimethamine, but very sensitive to mefloquine.

The development of resistance was noticed in eastern Zaire in 1983 (Delacollette). At the same period Mbuji Mayi and Kinshasa were shown to be free of chloroquine resistance (Nguyen Dinh et al., 1983).

In *in vitro* testing carried out that same year (Wéry et al., 1983) showed that *P. falciparum* exhibited normal sensitivity to chloroquine at Kinshasa, a slightly lower one at Lubumbashi, and even lower sensitivity at Katana. The same study revealed abnormal resistance to mefloquine only at Lubumbashi and a practically normal response to quinine in all three centres.

In 1984 at Kinshasa, Ngimbi et al. (1985) used *in vivo* testing for children aged 0 to 15 years and found that 5% of the cases of resistance was observed among the under-four group.

Finally, the *in vitro* tests using the three schizonticides were repeated in 1985 (Wéry et al., 1986). Increases in chloroquine and quinine resistance were seen in all three centres, Kinshasa, Lubumbashi, and Katana. Sensitivity to mefloquine was good, except in Lubumbashi, where the same resistance as in 1983 was observed.

### MEETING THE MAJOR CHALLENGES

1. **The parasite and its life cycle**

Malaria is a disease caused by a protozoon belonging to the genus *Plasmodium*. The plasmodium grows and multiplies in red blood cells and destroys them.

Four species of *Plasmodium* are pathogenic to man:
- *P. falciparum* is the most frequent and feared of the malaria parasites in Tropical Africa. It causes continuous, intermittent, recurring, or malignant (pernicious) tertian malaria, cerebral and renal involvement and in some, now extremely rare cases, blackwater fever. The pernicious attacks are characterized by serious cerebral complications: coma, with or without fever, convulsions (especially in children), mental confusion or delirium, etc. These are due to microthrombosis in the brain’s capillaries. If untreated, malignant malaria will generally lead to death.
- *P. vivax* causes benign tertian malaria with relapses because there are *hypnozoites* in the liver (dormant hepatic schizonts with slow development) which develop from some of the sporozoites injected by the Anopheles mosquito. This plasmodium occurs in foci throughout practically all climatic zones of Tropical Africa.
- *P. ovale* is similar morphologically to *P. vivax*, for which it is sometimes mistaken. It also causes benign tertian malaria. It is widespread in Central and West
Africa and most likely has an animal reservoir (certain primates such as chimpanzees).
- *P. falciparum* causes quartan malaria or fever. It has the same distribution as *P. falciparum* but is characterized by less severe parasitaemia. It is rather frequent in infants and young children and can provoke a severe glomerular nephropathy or a nephrotic syndrome. It is also a parasite of chimpanzee.

These various species of plasmodia vary in frequency according to the age of the patient and the ecological conditions, particularly the temperature linked to the altitude of the area.

Life cycle of plasmodia

The gametocytes or sexual forms of the parasite ingested with human blood by a female Anopheles mosquito are fertilized in the mosquito’s body where they develop into sporozoites (sporogony). This evolution takes 9 to 35 days, depending on the plasmodium species and the outside temperature. The sporozoites migrate to the salivary glands and are injected into the human host’s blood via the insect bite (Fig. 1). They invade first and multiply asexually in the hepatocytes (exo-erythrocytic schizogony). This stage lasts 7 to 15 days in man (11 to 16 days for *P. malariae*; 6 to 9 days for *P. vivax*; 5 to 7 days for *P. falciparum*; and 9 days for *P. ovale*). After this stage merozoites are released to invade the erythrocytes, where they develop into schizonts. The schizonts in turn divide, releasing merozoites that will invade other red blood cells. Each schizogony leads to the destruction of red blood cells and the release of parasites into the plasma, causing the attacks of fever whose intensity depends on the density of parasites in the blood stream and the host’s tolerance. The interval between attacks is species-specific (48 hours for *P. falciparum*, *P. vivax*, and *P. ovale*; 72 hours for *P. malariae*).

Some of the merozoites develop into gametocytes after invading the erythrocytes. By being ingested by a female Anopheles the plasmodium’s biological cycle develops, and hence transmission continues. The schizonts and erythrocytic schizogony are responsible for the disease, while the gametocytes are responsible for its transmission by the Anopheles mosquito.

2. Distribution of the parasite and the vector in Zaire

2.1. Distribution of plasmodia in Zaire

All four species pathogenic to man are found in Zaire:
- *Plasmodium falciparum*, the agent of tertian malaria, is the most frequently observed species.
- *Falciparum* malaria occurs year-round in the equatorial zone with seasonal surges.
- *Plasmodium malariae*, causing quartan malaria, is less widespread, although fairly common in infants and young children. It is rarely reported by microscopy examination because of the low-level parasitaemia it produces.
- *Plasmodium vivax*, is practically absent in West and Central Africa given the high percentage of individuals who do not carry Duffy blood group antigens on the membrane of the erythrocyte, whereby the merozoites cannot enter the RBC.
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- *Plasmodium ovale* is easily mistaken for *P. vivax*, mainly because, like the latter, it causes characteristic granulation in the RBC's and their enlargement. It is uncommonly reported in Zaire. The animal reservoir is of no epidemiological importance for humans. Unlike *P. vivax*, it causes relapsing malaria.

The prevalence of the various plasmodia varies according to age of the host and environmental conditions, particularly altitude with its lower temperature.

2.2. Distribution of Anopheles mosquitoes in Zaire

Only a few of the hundred or so species of Anopheles found in Zaire are vectors of malaria. These are *An. gambiae*, *An. funestus*, *An. moucheti*, and *An. nili*. Their presence and reproduction depend on two main factors – hydrological conditions and the ambient temperature. Cold (due to altitude) is a major limiting factor, which explains why malaria is markedly less prevalent higher than 1,500 m above sea level. The risk of infection is very slight above 2,000 m.

*An. gambiae (sensu lato)* is the commonest of the Anophelines. It includes *An. gambiae (sensu stricto)*, *An. arabiensis*, and *An. melas*. The latter breeds in brackish waters of the coastal regions. The *An. gambiae* complex is, along with *An. funestus*, the major vector of malaria. The low-altitude regions constitute the most favourable biotope for the complex, which is no longer found above 1,900 m. The breeding places are generally small collections of standing water exposed to direct sunlight. Alluvial mining operations and faulty drainage systems in the low-lying areas provide additional breeding grounds for *An. gambiae*, whereas the dry season limits its proliferation.

*An. funestus* is less uniformly distributed than the *An. gambiae* complex. It can be the dominant species in some areas (Lake Mobutu, Lubilash, Mayumbe, Rutshuru, Rusizi Plain). The grassy banks of streams and rivers are its favourite habitats. The species is generally more frequent in the countryside than in towns and cities.

*An. moucheti* is found at low and medium altitudes. It lives along the Zaire river and the lower Kwango river, and is basically a riverine species.

*An. nili* may be found at low and medium altitudes, along rivers, often in association with *An. moucheti* and *An. funestus*.

The marshy or poorly-drained valleys of the high plateaux can become major Anophelines-infested areas. This can lead to sudden outbreaks of malaria epidemics in non-immune populations, for instance in Rwanda and North Kivu. Hence the considerable impact of water and agricultural engineering on the incidence of malaria through its influence on the density of the anopheline population.

3. Endemicity: clinical and serological

Malaria has always been widespread in Zaire. It is not easy to estimate accurately to what extent it has been and continues to be responsible for general and infant mortality in this country. While malaria may be the direct cause of death, it can also raise mortality by weakening the body, making it an easier prey for other diseases.

Before 1905 – the year during which prophylactic quinine started to be widely spread – the African pioneers paid a heavy tribute to malaria and one of its serious complications, blackwater fever. However, exact figures for this period are not available.

Anyone living in an endemic area will be infected by malaria, but the intensity of the infection and the degree of immunity and tolerance is variable according to the individual reaction of the host. Among six-month to three-year old children, on the basis of a compilation of the statistics from several studies, *Duren* (51) estimated the mortality due to malaria at 14 to 22 per thousand. Duren found also that the specific fatality rate due to malaria dropped gradually between 1915 and 1950, while the part played by malaria in general mortality increased. This apparent increase can be explained by improved medical reporting based on a better understanding of the causes of diseases and death.

Epidemiological studies of malaria have undergone changes over the years. Initially based on parasite, spleen, and gametocyte rates, these elements were the basis of paludometry. They now include sero-epidemiological criteria.

a) Clinical paludometry

- The *parasite or plasmodic index* is obtained by examining thick blood films from a sample population or a defined age group for the presence of the parasite. The result is expressed as the percentage of positive thick films;
- The *transmission index* is the proportion of infants less than 1 year with parasitaemia;
- The *gametocyte rate* gives the number of individuals carrying gametocytes in a given sample of a population;
- An enlarged spleen is a characteristic symptom of malaria. The proportion of subjects with enlarged spleen in a given population is the *spleen rate*. This is a less specific index than the parasite rate, and comes at a later stage.

*Hackett's index* gives the average degree of splenic enlargement in a sample population of children aged from two to nine years. It is calculated using the following equation:
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(number of individuals in each class) x (the corresponding spleen enlargement coefficient)
Hackett's index = -----------
number of individuals with an enlarged spleen

The index is a measure of the average parasite density in the age group to which the subjects examined belong and thus reflects the intensity of the infection. It depends on the subjects' protective immunity and therefore reflects the stability of the disease throughout the time that this immunity has been maintained.

The degree of spleen enlargement can be measured. The organ's edges as palpated must be situated with respect to anatomical markers -- the costal margin, the navel and the antero-superior iliac spine.

The degree of enlargement is ranked on a 0 to 5-point scale as follows:
0 = spleen not palpable;
1 = spleen palpable on inhalation;
2 = spleen extending beyond the costal margin;
3 = spleen reaching the horizontal line through the umbilicus;
4 = spleen midway between the umbilicus and the left anterosuperior iliac spine;
5 = spleen reaching the left iliac fossa.

b) Sero-epidemiology is based on the value of the average antibody titre in a sample group. The more frequent and intense a person's contacts are with the parasite, the higher is his antiplasmodium antibody titre. The average antibody titre for a given population sample is therefore a measurement of the parasite inoculation rate and its propagation over the community. If by control measures the endemicity is lowered, the mean antibody titre will drop immediately.

The Indirect Fluorescent Antibody (IFA) test is the method most in use today. It has been the parasitological reference method in this field, as in many others, since 1965 (Demetrots and Wéry, 1985; Wéry and Le Ray, 1983). Enzyme-linked Immuno-Sorbent Assay (ELISA) methods have the advantage of speed. Their adaptability to automation is invaluable to reach unbiased readings and to process large numbers of samples (Demetrots et al., 1986).

The antigens used in any sero-epidemiological study must be homologues of the prevalent species of P. falciparum, P. vivax and P. ovale, P. malariae or to its simian homologue P. brasilianum (Benzerroug et al., 1986).

The severity and the stability of endemic malaria depends, first on the activity and efficacy of carrier mosquitoes (number of inoculated sporozoites per person and per day), and secondly on the receptivity of the individuals to infection. The point here is that each mosquito bite may cause a new infection.

The stability of endemic malaria depends mainly on the type of climate and on the peculiarities of the carrier mosquito species.

a) The simultaneous influence of high temperatures shortening the sporogony, the long lifespan of the Anopheles mosquitoes, and the frequency of their bites on humans (anthropophily) have as consequence that each mosquito is able to transmit the infection to a greater number of people. The number of Anopheles does not need to be very large to keep the inoculation rate high. Fluctuation of the number of mosquitoes will have little influence on the intensity of transmission. Hence, the incidence of malaria remains stable, as a lower rate of transmission has only very little effect on the endemic situation, as a state of saturation exists.

b) In contrast, unstable malaria is often the result of a cooler climate, a shorter Anopheles lifespan, or even, a lower preference of the mosquitoes for human blood (zoophily). In areas such as the Sahel high plateaux, or some islands, any climatic change or any variation in the extent of the Anopheles population will necessarily bring about an appreciable change in malaria endemicity. Any decrease in transmission will entail a decline of the infections in the population. The vectorial capacity of the Anopheles mosquitoes would decrease, but would have no effect at all on the prevalence of the infection in the humans.

WHO has adopted the following classification of endemicity based on the spleen rates or splenic index) observed in a statistically significant sample of population:
- Hypo-endemic malaria: spleen rate below 10% among children from 2 to 9 years old.
- Meso-endemic malaria: spleen rate between 11 and 50% among children two to nine years old.
- Hyper-endemic malaria: spleen rate above 50% in children from two to nine years old; the spleen rate in adults is also high (more than 25%).
- Holo-endemic malaria: spleen rate consistently above 75% in children between two and nine years old; a low spleen rate in adults.

Adults are included in the last two categories because intense perennial transmission leads in holo-endemic areas to considerable stable immunity in adults.
4. The disease

4.1. Clinical features

This disease is characterized by acute fever attacks and/or chronic manifestations such as anaemia and hypertrophy of the spleen.

4.1.1. Simple acute attacks

The attacks of fever are usually preceded by precursor signs of general discomfort such as shiverings, headache and nausea. The typical malarial attack, which lasts six to twenty-four hours, consists of three stages:
- it starts with a chill in which the temperature climbs to 40 degrees Celsius or higher,
- followed by the hot stage, in which the temperature remains high,
- and finally the fall of the fever, which is accompanied by profuse sweating.

The classic description of tertiary and quartan fevers, corresponding to the causal plasmodium, rarely matches the field reality. First, the primary invasion stage is characterized by rather uneven fevers; secondly, infections involving mixed plasmodium populations are the rule in holo-endemic countries.

The succession of erythrocytic schizogonic cycles every 48 hours for *P. falciparum* causes the blood parasite level to rise first to microscopically detectable levels (asymptomatic parasitaemia) at which parasites can be detected by microscope (depending on the quality of the instruments and microscopist), then to levels above the clinical threshold, at which point fever develops, (Fig. 2) and finally to the level of *pernicious* (algid) malaria, which can cause death. The immune system of individuals who live in endemic areas and are regularly infected by plasmodia develops a form of resistance that slows the parasite’s reproduction. In this case clinical attacks become rarer and parasitaemia persists at lower, asymptomatic levels.

Fig. 2 – Evolution of parasitaemia
The development of this immunity parallels changes in the size of the spleen, which in endemic areas becomes palpable at about 6 months, when the infant loses the protection of his mother's antibodies. In the absence of prophylaxis this splenomegaly persists until puberty or adolescence with some regional exceptions. Its regression corresponds to the acquisition of a more or less solid state of immunity, at which point the parasites are absent or very rare in the blood smears and the IgG and antiplasmodium antibody titres - the latter represent only a part of the total IgG - are elevated.

4.1.2. Subacute forms

The subacute forms testify to the absence of strong immunity. The tendency is to include under the term subacute malaria all the vague clinical pictures characterized by a course progressing over several weeks or rarely several months, with graded seriousness. The low-profile minor visceral malaria described in imported cases (Charmot, 1988) has not yet been evaluated in endemic areas. The high specific antibody titres that characterize this form cannot be used as a discriminating criterion.

At the other end of the scale of seriousness we have the subacute form formerly called progressive visceral malaria. This is a serious situation marked by a combination of anemia, asthenia, dyspnoea, weight loss, chronic fever or erratic attacks of fever, nocturnal sweating and gastro-intestinal disorders. Physical examination will reveal often severe splenomegaly whilst blood examinations will reveal haemolytic anaemia, elevation of the IgM and IgG due to the rise in antiplasmodium antibodies, and above all the sign of persistent infection disclosed by P. falciparum parasitaemia. This subacute form is encountered primarily in children under 15 years of age and causes a considerable number of deaths.

4.1.3. Tropical splenomegaly syndrome

Tropical splenomegaly syndrome (TSS) or malarial splenomegaly with macroglobulinaemia or malarial hyper-reactive splenomegaly is the syndrome that used to go by the name of tropical splenomegaly.

In 1 to 4 % of adults, a splenomegaly of impressive size can develop invading the entire left hypochondrium and persist; it is accompanied by anemia, tachycardia and moderate hepatomegaly without fever or jaundice and without signs of portal hypertension. Without treatment the evolution is slow but unfavourable: death, often due to infection, follows within five years of the diagnosis in 35-50% of the subjects.

Laboratory work will document the anaemia accompanied by neutropenia and thrombo-cytopenia. Isotope studies show a high degree of RBC sequestration in the spleen, as high as 20-25% of the total RBCs, hence the drop in their circulating pool. The bone marrow is rich and lymphocyte proliferation is sometimes found. The sedimentation rate is greatly increased. The main immunological event is the increase in IgM antibodies, which are polyclonal and non-pathological. Other immunological signs suggest the presence of circulating immunocomplexes.

The IgG titre is only moderately elevated compared with control titres. On the other hand, the titres of the anti-P. falciparum antibodies, the bulk of which belong to the IgM class, are very high, despite the usual absence of parasites in the circulating blood cells.

Tropical splenomegaly was long considered idopathic. There are many arguments in favour of a malarial aetiology, including a geographic distribution, concurrently with the distribution of hyper- and holo-endemic malaria and its usual but irregular response to long-term administration of schizonticides; proguanil, 100-200 mg per day, is standard (Onuigbo and Mbah, 1992).

The distinction between subacute malaria and TSS is not always easy to make. Moreover, transitional forms also exist. In subacute malaria the infection is steady (parasitaemia and fever), the IgM titre is only slightly elevated and the immune response is normal. In the case of TSS, hyperproduction of IgM and anti-P. falciparum IgM antibody signals the opposite of acquired resistance, which is an immune disorder.

TSS poses some complex immunopathological problems and interpretation of the condition has spawned a number of hypotheses concerning the role of plasmodial antigenic variations in triggering an abnormal proliferation of B lymphocytes that would induce the synthesis of abnormal globulins. For example, I. Bates (1991) found lymphocyte proliferation in 10% of the cases she studied in Ghana that made it difficult to differentiate TSS from Chronic Lymphoid Leukaemia (CLL). This is all the more difficult as some typical forms of the disease become resistant to antimalarials, in which case one may come across clonal rearrangements in the gene that codes for the immunoglobulins. One may surmise from this fact and from the monoclonal lymphocyte proliferation observed in some intermediate forms, that TSS may turn into malignant lymphocyte proliferation.
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Table 1. Progressive Visceral Malaria (PVM) versus Tropical Splenomegaly Syndrome (TSS), from Charmot G. & André L.J., 1977.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Parasitology</th>
<th>Immunology</th>
<th>Response to schizonticides</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tick drop</td>
<td>High IgM</td>
<td>Specific antibody titre</td>
</tr>
<tr>
<td>PVM</td>
<td>&lt;15</td>
<td>Intra-erythrocyte mal. pigment</td>
<td>Slight</td>
<td>Intermediate (esp. IgG)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fairly rapid</td>
</tr>
<tr>
<td>TSS</td>
<td>&gt;15</td>
<td>0</td>
<td>Strong</td>
<td>High (mostly IgM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slow</td>
</tr>
</tbody>
</table>

4.1.4. **Severe forms**

Severe forms of malaria are always caused by infection with *P. falciparum*, which can cause preferably in non- or poorly-immune subjects in just a few days the typical clinical picture of *pernicious malaria*. This term was formerly used for neurological forms complicating *P. falciparum* malaria. But WHO experts preferred to widen this definition to other manifestations of visceral failure, to attest the severity of the prognosis in order not to delay emergency intravenous treatment. It includes massive RBC destruction and involvement of the vital organs. The pathophysiology of this form is not totally clear. Sequestration of the parasites in the capillaries with release of vasoactive and thrombogenic substances should be leading to thrombosis and infarction and thus anoxia of the deep vital organs, especially the brains and the kidneys.

The following signs, isolated or associated, are criteria of severe pernicious malaria:

a) **Anaemia, haematological alterations and cardiac failure**

Severe anaemia leads to dyspnoea coupled with tachycardia, both caused by anaemia and the concomitant fever. The conjunctive membranes are extremely pale (the degree of anaemia is minimal in simple attacks; clinically detectable anaemia marks either urgency or a chronic infestation). Severe thrombopenia always accompanies these severe forms, although it rarely gives rise to haemorrhages; if they do occur, haemorrhages tend rather to result from disseminated intravascular coagulation (DIC). The intensity of the thrombopenia seems to be one of the best indicators of seriousness.

The signs of cardiac failure are all the more frequent if there is concomitant sepsicaemia.

b) **Cerebral malaria**

Cerebral malaria *stricto sensu* is characterized by coma, and repeated attacks of generalized convulsions or, less frequently, foci of localized brain activity. Cerebral involvement such as unconsciousness, is frequent in severe malaria, specially in children and pregnant women. If they survive, the children may be neurologically impaired.

c) **Renal involvement**

Renal involvement in case of *P. falciparum* malaria consists of oliguria and dark urine sometimes resulting from haemoglobinuria (or blackwater fever, covered especially pp. 1490-1508, because of its importance).

d) **Hepatic, pulmonary and gastro-intestinal involvement**

- Jaundice is due to both hyperbilirubinaemia following haemolysis and hepatic involvement.
- Hypoglycaemia, which results from depressed hepatic neoglucogenesis and an increase in sugar consumption by both the host and the parasite, is frequent and the prognosis is subject to caution.
- Pulmonary involvement leads to dyspnoea with polypnoea that is indicative of the pulmonary oedema that often occurs after several days of treatment. The oedema may reflect direct infestation of the lungs by the parasite or an excess of fluid. See also p. 1192.
- Gastro-intestinal signs such as uncontainable vomiting and profuse diarrhoea, are not rare.
- Algid malaria (hypotension, coma and shock) is the result of all these metabolism impairments. It may be attributable to secondary Gram-negative infections.

**Biological signs**

These allow to measure objectively the high levels of parasitaemia (more than 5% of the erythrocytes are infected by asexual forms), anaemia, renal involvement with elevated urea and creatinine, hypo-
glycaemia (often below 0.40 g/l), lactic acidosis and elevated amino-transferases (transaminases), depending on hepatic involvement, which exists in almost all cases of *pernicious* malaria. In the latter, elevated bilirubin and depressed synthesis of clotting factors and cholesterol are frequently seen.

**Prognosis**

These severe forms have a very bleak prognosis if they are not treated, especially in children; these account for the largest number of the fatalities. Malaria is believed to kill worldwide an estimated one million children a year and is the leading cause of febrile convulsions in Sub-Saharan Africa.

4.2. **Particular clinical forms**

4.2.1. Malaria and pregnancy

Malaria is an important cause of foetal death. In hyper- and holo-endemic areas malaria causes low birth weight, but the mothers often remain asymptomatic despite a high level of placental parasitaemia, as the placenta’s microcirculation is the seat of sequestration of parasitized red blood cells (RBCs). In areas where transmission is unstable pregnant women may develop severe infections with elevated parasitaemia, anaemia, hypoglycaemia and acute pulmonary oedema leading to high mortality. As a consequence foetal distress, premature labour and stillbirths are often seen in such areas. The importance of this infection during pregnancy is linked to its characteristic immunosuppression, the mechanism of which is still poorly understood.

4.2.2. Congenital malaria

Congenital malaria is rare, although the parasite is detected in 20 to 30% of the cord blood samples of infected women. It does not have considerable importance, since conditions in the newborns are not favourable for the development of the infection. Infants are protected by their mothers’ antibodies up to three to six months and foetal haemoglobin (HbF) is less easily utilized than haemoglobin A (HbA).

We can draw a connection between the influence of the presence of abnormal haemoglobin and the difficulty for plasmodiums to make use of HbF in thalassaemia or HbS in Sickle cell anaemia. The same applies to glucose-6-phosphate (G6PD) deficiency, which also hampers the parasite’s development, as it needs this enzyme to mature.

4.2.3. Transfusion malaria

Transfusion malaria is a particular way of transmission by injection of parasitized red blood cells. The incubation period is shorter than in the case of infection by a mosquito bite since no pre-erythrocytic stage is necessary.

In the absence of the hepatic cycle the parasites simply continue multiplying in the recipient’s blood. In endemic areas it is impossible to monitor parasite levels in blood donor. Consequently, all transfusion recipients should be given a curative dose of a schizonticide. Donors potentially infective in non-endemic areas are detected by means of questioning and sero-testing. If no screening has been performed, the possibility of transfusion malaria should be considered for diagnosis when a febrile syndrome develops, although such a febrile syndrome is often difficult to attribute to malaria as it is usually not noticed by the patient. Transfusion malaria can be very serious as it commonly develops in a subject weakened by the condition requiring the transfusion.

4.2.4. Malaria in children

This form of malaria deserves special attention because of its frequency and seriousness, even though attacks in endemic areas are rare before the age of three to six months, given the protection afforded by the mother’s antibodies. After this cut off age *P. falciparum* malaria is the leading cause of febrile convulsions and a significant cause of *childhood diarrhoea*. Its severity is increased by malnutrition and anaemia, which it exacerbates in turn, justifying presumptive treatment, which means without prior thick film result (see below the treatment of malaria attacks in infants p. 1463). If not treated the disease often progresses to extremely serious forms, including *pernicious malaria*.

The characteristics of *pernicious malaria* in children are slightly different from those in adults. Onset with a cough is frequent, the initial parasitaemia is high, hypoglycaemia occurs early in the course of the disease, neurological signs (convulsions) are extremely frequent, and the patient drops very quickly into a coma. In the absence of treatment, the success of which is limited, death occurs in one or two days. Finally, 10% of the survivors have neurological sequelae.

- *P. vivax* malaria tends to give rise more readily to febrile, anaemic cachexia.
- *P. malariae* malaria can lead to *quartan nephritis*, which is a severe glomerular involvement that is often revealed by a nephrotic syndrome.

4.3. **Diagnosis**

a) The clinical diagnosis is classically based on the attacks of fever, anaemia and splenomegaly. However, some of these signs may have several aetiologies and
often lack clarity as well. In attacks during a primary infection the degree of anaemia is very slight and the spleen becomes only gradually enlarged. The only sign that might give a clinical clue is the development of a periodicity in the fever (tertian, quartan). However, this periodicity is not constant, especially in the case of *P. falciparum*.

b) The diagnosis is in fact only *parasitological*.

The thick film technique is some twenty times more sensitive than the blood smear technique. However, the former requires perfect technique to prepare it, whereas the latter has the advantages of prior drying with much quicker staining than the thick film, thus saving time, and above all showing the parasites’ morphology much more clearly, making it possible to identify the species involved; this is all the more important in case of *P. falciparum* infection, since the severity of the disease it causes and the possibility of resistance to the usual medicine must be taken into consideration.

Still, interpreting these tests calls for a few remarks, for it is fraught with difficulty in the field:
- the sensitivity of the test requires a large number of parasites: threshold of 250 million parasites in the body must be crossed if the microscopist is to detect them in a thick film. As a result, a negative thick film does not necessarily mean the subject is disease-free. In addition to detect parasites in chronic subacute malaria, several thick films must be read. On the other hand, the sensitivity of the thick film technique in the case of classic attacks is such that a negative result allows to rule out nearly certainly malaria as the source of a high fever. Still, a thick film test can be negative in acute attacks if the *P. falciparum* parasites develop synchronously and have reached all the schizont stage of development, being thus sequestered in the viscera at the time that the specimen is taken. It is obviously very difficult to prove that a fever is due to malaria if the parasite cannot be detected, especially since sero-testing is useless for an individual in an endemic area.

Whereas the thick film test’s sensitivity is almost 100% in the case of *P. falciparum* attacks, it is much lower for infestations by other species of the parasites. *P. malariae* and *P. ovale* are known for their very low-level parasitaemia, even in impressive, completely typical clinical pictures. Consequently, the tertian or quartan periodicity of the fever may be a sufficient reason for instituting treatment even if the thick film test remains negative.
- the specificity of the test, which ideally should indicate a parallel for the parasitological and clinical elements, must be interpreted as follows:

1. in clinical medicine one should never forget the fact that what is looked for in the thick film is the cause of the patient’s clinical condition; for example, a slightly positive thick film is but a very poor argument to explain a serious clinical state in a semi-immune patient; other possible causes must be considered without overlooking the presence of the parasite;
2. for the epidemiologist, the presence of parasites in the blood of the inhabitants of a (holo)endemic region is not necessarily synonymous with morbidity. In some towns in Sub-Saharan Africa 50 to 60% of the children up to the age of ten years and 25% of the adults are clearly carriers of the blood parasites, yet they are not ill and lead practically normal lives. The immunity acquired by Africans is efficient and detection of plasmodia in their blood (positive thick films) is by no means a sign of illness. Actually, weakly positive thick films are not all taken into account. However a quick increase in parasite number from one to a next blood sample points seriously to the diagnosis of malaria.

Practically in endemic areas:
- it is impossible to confirm all malaria attacks by microscopic examination; this would waste too much time before action; it would increase considerably as well the morbidity figures as the mortality by delay in treatment; rapid treatment based on a presumption of infection must be the rule.
- sero-testing has no diagnostic value for individuals in endemic areas; it is not useful for primary invasions, for at the start of the attacks antibodies are either absent or present at too low a titre to be detected.
3. sero-tests do allow retrospective diagnoses in the event of imported cases; they also enable to screen for some potentially dangerous blood donors; however, their greatest utility is in the field of sero-epidemiology (see p. 1454).

5. Recent advances

5.1. Titration of anti-sporozoite antibodies

Chemical synthesis of the major sporozoite antigen, a tetrapeptid, made possible to measure the titres of the antibodies directed against this antigen.

The amount of antibodies is related to the frequency of contact with the sporozoites, and thus gives a measure of the inoculation rate (frequency of infective bites).

5.2. Sporozoite detection in Anopheles

The contribution of immunology to epidemiological studies does not stop here. Indeed, the Zavala test using monoclonal anti-sporozoite antibody has made
it possible from 1987 onwards to detect sporozoites in an Anopheles mosquito without dissecting the salivary glands. This immuno-enzyme test is available in a simple field kit. It could provide important information on malaria vectors in endemic areas and help malaria control officers to choose the appropriate vector control measures against the dangers of infection (Zavala et al. 1982).

5.3. Parasite detection in blood

Parasite detection in blood samples has benefited from advances in molecular genetics. A fraction of plasmid DNA that is purified, then denatured, can be used as a probe to detect the presence of DNA from a homologous species in parasitized blood. This DNA hybridization technique is based on recognition by the reference DNA of a specific DNA sequence in the plasmid species which is being sought in the patient’s blood. At present the field use of this technique is hampered by the need to mark the probes with radioactive isotopes; however, consideration is being given to other markers of probes, especially to enzymes. These techniques will allow detection of very low levels of parasitaemia in the field and perhaps replace thick film microscopic examination.

6. Measures to control malaria

The strategy of malaria control is to break the chain of transmission either by destroying the parasite in the human body or by preventing infection by the anopheline vector.

Antiplasmodial compounds may be used for prophylaxis or treatment. As there is no drug of low toxicity available to prevent the exo-erythrocytic forms responsible for the human infection to settle and develop in the liver, the aim to prevent the disease is to limit the proliferation of parasites in blood. The objective is to prevent both the clinical symptoms and transmission to the intermediate hosts, that is, the Anopheles mosquitoes.

Vector control is possible by destroying mosquito larvae in stretches of water in which the eggs may be laid.

Adult anopheline vector control strategies can be divided into passive protection of man from mosquito bites (screens and netting) and active control using residual insecticides, mostly as residual household sprays.

6.1. Active drugs, development in the time

a) In the Congo (Zaire) at the beginning of the century the first successes against malaria were due almost exclusively to the use of active propaganda campaigns to spread the preventive use of quinine. Quinine limits trophozoite multiplication, lowers considerably the frequency of attacks and reduces their severity when they occur; whereby quinine helps the host to get a premunition. Mass quinine prophylaxis leads to a marked reduction in the infection rate of the Anopheles population and thus the endemicity of malaria.

The recommended prophylactic dose was 250-500 mg per day for adults. Absorption is rapid, but so is its clearance, requiring strict observance of the daily dosage regimen.

As a curative treatment, quinine is used for an adult at the rate of 1,500 to 1,800 mg per day, given orally during five to seven days divided over three eight-hourly intakes. For complicated cases involving coma and vomiting the product will be injected, preferably intravenously.

Cinchona plantations were planted in several parts of Zaire at Rodhain’s suggestion. The red cinchona (Cinchona succirubra) gives the most robust plants in the northeast, but the bark of the yellow cinchona (Cinchona ledgeriana) is the richest in quinine. Hybrid forms (root of Cinchona succirubra grafted on a C. ledgeriana stock) have been grown with encouraging results. Although decoctions of cinchona bark (Totaquina) might be expected to have prophylactic or curative effects, there are serious drawbacks both in terms of the amount of active principle actually ingested and certainly as to their therapeutic effects, due to the variable concentrations of quinine therein, as well as to the presence of other alkaloids. It is therefore preferable to use quinine in the form of salts.

Quinidine has the same schizonticidal action as quinine.

b) The first synthesized antimalarialis (Atebrin® and Plasmochin®) came on the scene in the twenties and thirties. The scarcity of quinine during World War II led to the switch to Mepacrine (Atebrin®) in prophylactic and curative therapy. This very powerful compound had nevertheless a few drawbacks, such as yellow skin pigmentation, lichen planus, mental and cardiac side-effects.

c) Chloroquine, which is a 4-aminoquinoline, made its appearance after the Second World War. This blood schizonticide has a slower but more prolonged action than quinine. Curative doses for adults range from a single 600 mg dose to 2,500 mg administered over three or four days, depending on the subject’s immunity and the parasite’s resistance.

Chloroquine resistance

Cases of chloroquine-resistant P. falciparum attacks have been reported since 1961. In Africa, these resistant
strains first appeared in the eastern part of the continent around 1979, and are continuing to spread westwards.

When resistance of *P. falciparum* to chloroquine appeared it was greatly disappointing. However the use of chloroquine should not be discarded before unbiased evaluation of its activity. Resistance can be very different from one country to another and even within the same country; therefore its sensitivity or resistance must be determined *in vivo* according to WHO’s grading (S, SRI, RI, RII, RIII) and if possible confirmed *in vitro* by comparing the degree of inhibition for the maturation of parasites in control samples of blood with that observed in samples containing chloroquine (Inhibiting Concentration IC₅₀).

There are two types of tests for recognizing *P. falciparum*’s resistance to chloroquine, *in vivo* field tests and *in vitro* tests:

- **a) field tests in vivo:** after three days’ treatment with chloroquine base (25 mg/kg),
  1. If no asexual parasite are found on thick films by Day 6 and none are present on Day 7, the infection may be either sensitive (S) or resistant (R) at the first stage of resistance or R I level.

When fresh infection can be excluded for 28 days, failure to detect the return of parasites by Day 28 using the extended test, indicates that they are sensitive.

**Table 2:** Grade of resistance of asexual parasites of *P. falciparum* to schizonticidal drugs (4 aminoquinoines)

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>S</th>
<th>Clearance of asexual parasitaemia within 7 days of initiated treatment, without subsequent recrudescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance</td>
<td>RI</td>
<td>Clearance of asexual parasitaemia within 7 days, followed by recrudescence</td>
</tr>
<tr>
<td></td>
<td>RII</td>
<td>Marked reduction of asexual parasitaemia but not clearance</td>
</tr>
<tr>
<td></td>
<td>RIII</td>
<td>No marked reduction of parasitaemia</td>
</tr>
</tbody>
</table>

(from WHO, 1986)

2. If asexual parasites disappear for at least two consecutive days but return and are present on Day 7, they are resistant at the RI level (7-day test). When fresh infection can be excluded for 28 days, any asexual parasite recrudescence within 28 days indicates an RI response.

3. If asexual parasitaemia is not cleared up but reduced to 25% or less of the original pretest level in the first 48 hours of treatment the parasites are resistant at the RII level.

4. If the asexual parasitaemia is reduced by less than 75% in the first 48 hours, remains stable, or continues to rise, the parasites are resistant to the standard dose of the drug at the RII level.

b) *in vitro* test: the maturation of the parasites is inhibited by 4-aminoquinoines such as chloroquine and amodiaquine, and by dihydrofurole-reductase inhibitors such as pyrimethamine, cycloguanil and proguanil. The extent of this inhibition can be assessed by comparing the degree of maturation in control samples of blood with that observed in samples containing the drug. The percentage of ring forms that mature to normal-looking schizonts which contained more than two nuclei, provides a useful endpoint for the quantitative assessment of maturation.

Preliminary results have shown a good correlation with the *in vivo* test, especially as regards sensitivity and RI and RIII resistance. However, more field studies in which the *in vitro* and *in vivo* tests are performed in parallel are required to ascertain to what degree the *in vitro* test is a dependable indicator of the level of drug response in a given area. (WHO, Chemotherapy of Malaria, 1986.)

Today’s possible supply of chloroquine at the most advantageous price, although mostly without quality control, dictate to remain very careful in the evaluation: the test must be done on a ratified substance for its chemical composition and its quantity per tablet.

One must also take in account that chloroquine would in any case remove a good part of the parasites of a strain with resistance RI or RII and that the product remains active against *P. vivax*, *P. ovale* and *P. malariae*.

Chloroquine will still remain for a long time the basic antimalarial medicine for the greatest number of malaria foci.

*P. falciparum* has also exhibited resistance to other synthetized antimalarials, viz., paludrine, pyrimethamine, sulphones and sulphonamides, making malaria prevention and even treatment increasingly difficult.

d) Proguanil (Paludrine®) is active against the pre-erythrocytic stage of *P. falciparum*, the dominant species in Central Africa, and has also a schizonticidal activity in blood. It appears to have negligible toxicity. As it is less active than other antimalarials, it is not recommended for curative therapy, but remains useful for prevention in individuals (100 mg per day), although cases of resistance have been reported in some parts of Southeast Asia and Africa. The prophylactic dose may be increased to 200 mg per day.

e) Primaquine, an 8-aminoquinoline, prevents relapses due to *P. vivax* or *P. ovale* by destroying the hypnozoites that these species produce. Dosage regimens for adults are 15 mg per day for two weeks or 45 mg per week for six weeks. This drug is also active against the gametocytes, especially those of *P. falciparum*. However, it has a schizonticidal action only at doses close to toxic doses. This toxicity is manifested primarily by methaemoglobinemia and renal obstruction.
due to deposits of crystals of haemoglobin. Moreover, primaquine causes haemolytic attacks in glucose-6-phosphate dehydrogenase (G6PD) deficient subjects, who are numerous in sub-Saharan Africa. As it is suitable only for forestalling relapses due to *P. vivax* and *P. ovale*, it is not much used in endemic areas.

f) Pyrimethamine (*Daraprim®*), whose activity is comparable to that of proguanil, has the advantage of being active in low doses (50 mg per week for prevention). Many strains of *Plasmodium* are resistant to it.

g) Today the preferred practice is to use it in combination with a sulphonamide (*Fansidar®*) or a sulphone (*Maloprim®*). Sulphonamides and sulphones are not used alone. Their combination with pyrimethamine potentiates the latter’s action, so much the more that many *Plasmodia* strains are resistant to pyrimethamine, if given alone. *Fansidar®,* the combination of sulphadoxine 500 mg and pyrimethamine 25 mg, per tablet is given as a single intake of 3 tablets for an adult. *Maloprim®,* the combination of dapsone 100mg and pyrimethamine 12.5 mg, has, in fact, not a very reliable efficacy and has toxic side-effects in long-lasting treatments.

h) Mefloquine (*Lariam®*) is a recent compound with a formula similar to that of quinine but a much longer-lasting action. It is used in undivided doses of 250 mg per week for prevention in countries where chloroquine resistance is prevalent. To treat acute attacks, 1,500 mg (adults) are given in three divided doses. There are some foci in which mefloquine’s efficacy was from the onset lower than normal, such as in the area around Lubumbashi in Shaba (Zaire); this was discovered by chance during *in vitro* testing (Wéry *et al.*, 1985, 1986).

i) Halofantrine (*Halasan®*) is a new drug for which clinical testing has been concluded. It is used for treatment in one time dose of 1,500 mg spread over 18 hours, and the course may be repeated one or two weeks later, where patients are not immune. No evidence is available at present that it can be used for prophylaxis.

j) Artemisinin (qinghaosu) is extracted from a plant, *Artemisia annua*. This drug, long known in China for its antipyretic properties, has also very pronounced schizonticidal properties. Its action is of short duration but its toxicity seems low. Research is under way to synthesize derivatives of this new molecule for malaria chemotherapy.

The antimalarial properties of sulphonamides have been known since 1935, those of sulphones since the forties. The resistance of the plasmodia, especially *P. falciparum*, to the usual medicines has increased the importance of combining these treatments - The schizonticidal action of tetracyclines, which are broad-spectrum antibiotics, was recognized in the sixties. At the time, *P. falciparum* malaria attacks were cured completely by giving chlorotetracycline, 1 gm per day, for seven days. However, tetracyclines are administered only in conjunction with other antimalarials, especially quinine. This combined therapy saved many patients in the Far East when chloroquine-, *Fansidar*- and, to a certain extent, quinine-resistant *P. falciparum* strains appeared.
- Doxycycline was introduced in 1966 and microcyncline in 1972. These semi-synthetic tetracyclines are just as effective schizonticides as the original tetracyclines but have the advantage of being easier to handle; doxycycline in particular is less toxic for the kidneys than tetracycline. In combined administration with quinine the curative doses are for tetracycline 6 × 250 mg per day for 7 days and for doxycycline 2 × 100 mg (for adults) the first day, then 100 gm per day in a single dose for the next six days (see below treatment course).
- Clindamycin was used in countries where *P. falciparum* strains with multiple drug resistances were observed. Its schizonticidal action, especially on the circulatory forms and its not negligible activity on the hepatic forms, were recognized in 1972. It should be preferred over tetracyclines for patients with moderate renal failure. The curative dose is 8 to 10 mg per kg per day and *per os*, in four divided doses for 5 to 7 days. When it is administered by intramuscular injection or by intravenous drip the daily doses may be doubled, cutting the course of treatment down to 3 or 4 days. Combining clindamycin with quinine enables to halve the doses.

6.2. Treatment
6.2.1. Treatment of simple attacks

For attacks of malaria without encephalitic signs or signs of severe illness, including initial invasion or schizogenic revival and even subacute forms:
- a) in areas of known sensitivity and in the absence of *P. falciparum* resistance to amino-4-quinolines, chloroquine should be used in the following amounts:
  - previously unexposed subjects: 40 mg per kg over 5 days;
  - subjects with partial immunity: 25 mg per kg over three days (10 mg per kg the first two days, 5 mg per kg the third day).

Oral administration should always be preferred. In the case of vomiting, divided doses by subcutaneous or intramuscular injection should be given, except to children (p. 1463). Never should the dose of 3 to 4 mg per kg per injection be exceeded and as soon as possible one must switch back to oral administration.
b) in areas of known resistance to chloroquine and if resistance is suspected when fever fails to disappear by the third day (see other signs of resistance p. 1461) quinine should be used at the doses of 25 mg quinine base per kg body weight per day, in three divided doses (eight-hour intervals) for 5 to 7 days. The doses of quinine must be divided because quinine is cleared quickly, either eliminated or metabolized.

Oral administration of quinine is preferred whenever possible. Uptake per os is close to 100%, making this route equivalent to intravenous administration. In the case of vomiting, serious nausea and loss of consciousness the intravenous route is imperative. Intramuscular injections are to be avoided because they can cause aseptic necrosis. Only the severity of the clinical condition can justify an IM injection, which should be given preferably in the quadriceps muscle, before transfer to a hospital or if the patient cannot be transferred.

A complete course of quinine is difficult to tolerate because of its side effects; indeed, the majority of patients discontinue the treatment.

**Therapy with drugs associated to quinine**

Combining quinine with another drug makes it possible to shorten the course without reducing its efficacy:

1. Quinine + (sulfadoxine + pyrimethamine = Fansidar®)
   First day: quinine base three times 8 mg (= 10 mg of dihydrochloride) per kg body weight per day.
   Fansidar®: 1 tablet per 20 kg body weight
   Second through fourth day:
   quinine base three times per day 8 mg (10 mg dihydrochloride) per kg body weight.
   If the patient vomits or is nauseous the first day, one should wait until the second day to give the single dose of Fansidar®.

2. Quinine + tetracycline:
   For four days: quinine base three times 8 mg per kg body weight, and in addition:
   tetracycline three times 8 mg per kg body weight or doxycycline, a single 100-mg dose (in adults).
   In the case of vomiting or nausea, one should wait until the second or third day to add the tetracyclines.

The treatment is effective against strains with multiple drug resistance. Tetracyclines must not be administered to either pregnant women or children under eight years of age.

**Use of new drugs**

- **Mefloquine (Lariam®)**
  The drug cannot be used for children nor for individuals below 45 kg.
  One-time dose of 25 mg per kg, given in three doses over 24 hours. For an adult three 250 mg tablets are given at the start, then eight hours later 2 tablets of 250 mg, and again 8 hours later one tablet.

This drug has a lasting effect and is effective against most of the malaria strains. However, side effects are significant and are seen in 50% of the patients who receive the classic dose of 25 mg per kg per day, which is why the dose has been set to 20 mg per kg.

- **Halofantrine (Halphan®)**
  25 mg per kg are divided into three times 8 mg per kg at eight-hour intervals (or 500 mg three times over 18 hours for adults). The drug is effective against most of the malaria strains. It is recommended that the course be repeated after a week in non-immune patients. Uptake by the gut is irregular but can be improved by the simultaneous intake of food that is rich in fat.

6.2.2. **Treatment of attacks in infants**

Chloroquine should be given in doses of 10 mg per kg per day for two days, then 5 mg per kg per day on the third day for a total dose of 25 mg per kg. The injectable form is contra-indicated in children under three years of age. For three-year-olds and up it remains dangerous, as it can provoke cardiac rhythm disorders and failure. In the case of gastro-intestinal disorders one should use either quinine given intravenously in a glucose solution, or a single intramuscular injection of Fansidar® – 1/2 to 1 ampulla of 2,5 ml (ampulla containing 500 mg sulphadoxine and 25 mg pyrimethamine).

A chloroquine-resistant *P. falciparum* malaria attack should be treated by quinine drops, 8 mg of base (or 10 mg of dihydrochloride = 1 drop) per kg body weight every eight hours for seven days. In the case of gastro-intestinal disorders the same dose of the injectable form should be given intravenously in isotonic glucose, every eight hours, returning to oral route once the gastro-intestinal disorders have disappeared.

6.2.3. **Treatment of attacks in pregnant women**

A course of chloroquine should be instituted. If resistance is observed, quinine may be used. Following doses of quinine should be used for the first trimester and the last weeks of pregnancy: 1,500 mg of salt per day in three divided doses for seven days. Treatment from the fourth through the seventh month of pregnancy may consist of quinine alone (for seven days) or combined with Fansidar® which is not contra-indicated during this period.

Note that quinine does not have any abortive properties.

Mefloquine and halofantrine should not be administered to pregnant women because they have not been in use long enough to assess their safety.
6.2.4. Treatment of severe (pernicious) malaria

a) Anti-parasitic treatment

All attacks of pernicious malaria must be treated with quinine. In principle, the dosage is the same as for simple malarial attacks: 10 mg per kg three times per day in glucose solution by slow intravenous injection until the trophozoites have disappeared. The grounds for administering a loading dose are still open to discussion. According to some pharmacological studies (White, 1983), a loading dose should be given in order to obtain satisfactory concentrations right away. The administration of 20 mg per kg for the first four hours can be done according to various schedules:

Either 10 mg per kg for the first 30 minutes followed by 10 mg per kg for the next four hours or 20 mg per kg distributed over four hours.

The schedule for children is 15 mg per kg for the first four hours, then 5 mg per kg every eight hours, then 10 mg per kg for two days and finally 5 mg/kg for four days, always every eight hours.

Other authors would rather give the classic treatment, which is supposedly less aggressive and should reduce the signs of fierce destruction of the parasites.

The treatment with quinine should be continued until the last trophozoite disappears from the blood stream and should be backed up by Fasidimar® or tetracyclines (or halofantrine or mefloquine if they are available).

b) Supporting treatment to the patient

- Supporting treatment is imperative and includes to hydrate properly the patient and restore his electrolyte balance, taking in account the frequent hypoglycaemia episodes, which are responsible for more or less deep or extended comas and are accentuated by quinine. Blood sugar analyses should be performed regularly if one has access to a reliable laboratory. As a preventive measure quinine is administered intravenously in a glucose solution;
- the treatment also includes to give antibiotics so as to prevent superinfections, particularly lung infections and septicaemia; anticonvulsives such as phenobarbital and diazepam should be given, but also vasopressive amines in the case of cardiac failure;
- a certain degree of renal dysfunction occurs in almost all cases of algid malaria and usually responds well to medical treatment. Reducing the quinine doses in the case of oligo-anuria is open to discussion. The practical position is to maintain the normal dosage regimen for the first 24 or 48 hours, then cut it by 30 to 50% by spacing the doses over wider intervals if oligo-anuria persists; oligo-anuria itself should be treated by extrarenal filtration methods, only if this situation continues and the blood urea or creatinine level becomes dangerously high.

Haemodialysis cannot be performed in the field, while peritoneal dialysis has a proven efficacy, requiring a much less elaborate set up; however it exposes the patient in the tropics to infection.

Partial blood replacement by exsanguino-transfusion has been proposed for the twofold purpose of lowering quickly the parasite load and of eliminating the circulating toxins. This requires only a limited amount of equipment: two three-way valves, a femoral catheter and a pouch for collecting the blood. It allows blood transfusion of seriously anaemic patients without the risk of a fluid overload: this overload is not well tolerated at all, even if the chest X-ray is normal.

6.3. Prevention

Malaria prophylaxis is a complex problem that cannot be devised according to a rigid scheme. The action must be adapted to the subject’s age and immune status, to the level of endemicity, and to the local strains’ resistance to the drugs.

6.3.1. Individual prophylaxis

Prophylaxis schemes allowing for the areas of P. falciparum sensitivity and resistance to amino-4-quinolines can nevertheless be proposed for individuals who go to live in areas where malaria is endemic.

- In areas where the strains are chloroquine-sensitive and where the transmission rate is low: chloroquine, one 100-mg tablet should be given six days a week as of the day of departure (or in a 300 mg weekly dose for adults) and for one month after the return to a non-endemic area.

- In areas with highly-resistant strains (level R3): mefloquine should be used 0.250 gm per week for brief stays (less than 3 months), although if such monotherapy is used the development of resistance may be feared. For long stays the current opinion is in favour of refraining from preventive medication and treating all attacks of fever immediately with quinine or halofantrine or mefloquine.

- In areas of weakly-resistant strains (R2): chloroquine should be given combined with a daily dose of 200 mg of proguanil and the traveller should be informed of the possibility of treatment failure: all attacks of fever must then be treated like in the R3 areas.

6.3.2. Prevention for at-risk groups

In the early eighties it was often the practice to give to at high risk groups in endemic countries a preventive dosis of amino-4-quinolines in order to protect them of infection, especially for 6-month to five-year-olds. However, this approach is falling away for it is only effective in areas where P. falciparum is sensitive to chloroquine; it is also expensive and difficult to
organize, and above all carries the risk to single out resistant strains. It is no longer advised except for pregnant women (300 mg of chloroquine a week or fortnightly during the second and third trimesters of pregnancy).

Presumptive-treatment with chloroquine or curative doses to treat all fever incidents (25 mg per kg over three days) is preferred.

6.3.3. Vaccine research

An effective malaria vaccine may eventually be developed towards the year 2000. Research to induce an immune response has examined how to approach various stages of the parasite’s development. Study of immunity against sporozoites was started in 1967 by Ruth Nussensweig, who obtained animal protection by injecting them with X-rayed sporozoites. The serum antibodies of the protected animals reacted with a sporozoite membrane protein, the circum-sporezoite protein. Unfortunately, the results yielded by the only valid animal model, the chimpanzee, when \( P. falciparum \) sporozoites are injected to it are not very reproducible; it is the same when human volunteers are infected.

Research into vaccines aimed at the asexual forms in blood has yielded some good protective responses in animals using irradiated red blood cells (RBC) suspensions or emulsions with Freud’s adjuvant. The refinement of \( P. falciparum \) culture techniques allowed primate immunization trials using various stages of the human parasite. These trials produced rather good protection but also revealed the great complexity of the antigenic structures of these parasite forms in the RBCs.

This led to a diversification of the experimental approaches which tried to identify the protective antigens. The molecular structures of many of these antigens were established thanks to a deep study of the molecular biology of the malaria parasites. Recently excellent protection for the lemuroid \( Aotus \) sp. was observed and encouraging results in human volunteers using antigens that were produced by synthesis or genetic engineering (Patarroyo, 1988).

Further research is directed to anti-gametocyte vaccine. This was made possible by the ability to detect antibodies neutralizing the sexual forms of the parasite once they have been freed within the stomach of the mosquito. Still other investigations are directed to vaccines against exo-erythrocytic forms of the human parasite, as their culture was made technically possible.

Research is further developing on the fact that the response against erythrocytic malaria antigens seems seriously impaired by the major histocompatibility complex. But the mechanisms by which the parasites try to escape the immune response are not yet completely clarified. Many obstacles are still to be overcome before the composition of the best immunizing polypeptides can be defined.

7. Anopheles control

(see also the transmission factors relevant in Malaria vector control programmes, p. 1480)

7.1. Larval control

Breeding points can be eliminated by filling in swamps, draining collections of standing water, increasing or decreasing water salinity, or by planting stands of eucalyptus. Such interventions may occasionally entail major operations (drainage, straightening the banks of watercourses), and require a health policy that deals with stretches of water collected in the vicinity of dwellings.

The Anopheles larvae can also be destroyed chemically. Spreading gasoline—a method used for still water collections fairly free of vegetation—kills the larva by both asphyxiating them and by attacking their nervous system. Paris green (cupric acetoselenite) and DDT (dichloro-diphenyl-trichloro-ethane) spread as a floating powder on the water’s surface can also be used.

Larvivorous fishes may be used to destroy larve in appropriate habitats. Some good examples are gambusias and tilapias, as well as the extremely voracious year-round species of the family Cyprinodontides, which survive even when the surface waters dry up during the dry season.

7.2. Control of the adult vector

7.2.1. Passive protection

The healthy individual can protect himself by setting up his dwelling far from larval breeding places. Mountains at an altitude of 1,800 m. above sea level are generally free of Anopheles. Elsewhere the openings of houses must be covered by metal or, better, by plastic screens (these are more durable) with meshes approximately 1.2 to 1.5 mm in diameter. Mosquito bed nets are absolutely essential in all malarial regions. Mosquito nets soaked in insecticides of the pyrethrinoid group are becoming increasingly popular.

Various repellents can also be effective. In the past, citronella or eucalyptus oil was rubbed on the skin, but the protective action was brief (15 to 20 minutes). Today’s chemicals as indalone, dibutyl-phthalate (DBP), and diethyltoluamide (DEET) provide protection for several hours. Diethyltoluamide seems to be the most effective. It is used either as a 50 to 75% solution in alcohol, as a spray at 28%, or a gel at 15% and can also be used to coat some items of clothing and mosquito netting.
7.2.2. Indoor insecticide spraying

Although attempts have been made in Zaire to control adult Anopheles mosquitoes in the home by spraying with pyrethrin (e.g. 100 gm pyrethrin powder in a litre of gasoline), the strategy has turned out to be impracticable.

DDT is a contact poison that is lethal for mosquitoes and flies. The almost odourless white powder is practically insoluble in water, which accounts for its long-lasting action. Mosquitoes that come into contact with the particles in a DDT suspension are irritated, stop biting and die, generally within 24 hours. Using insecticides is an effective means of malaria prevention only if all the buildings and premises in the community are sprayed. A dose of 2 g DDT per m² will eliminate practically 100% of the adult Anopheles inside the house for three to six months.

Malathion is the next most frequently used insecticide for malaria control. It has a residual action lasting three to six months but a most unpleasant odour. It is fairly non-toxic for man.

Gammexane (HCH) has the advantage of being more toxic for insects than DDT, but the disadvantage of being toxic for man too. Moreover, resistance to this insecticide has been reported.

7.2.3. Outdoor insecticide spraying of breeding places

DDT (powder or suspension) has also been spread over the mosquitoes’ natural habitats by means of compressors carried by trucks, tractors, light aircraft, or helicopters. Such space-spraying strategies are strongly contra-indicated for ecological reasons and because they select resistant mosquitoes.

7.3. Control measures involving the population

Malaria control received general attention as early as the end of the nineteenth century in the form of individual protection for foreigners and, later on, for native children at infant clinics and schools. Although it was not until the early thirties that malaria was classified as one of the transmissible diseases requiring systematic control, various statutory measures had been taken before that time, such as the elimination of pools of stagnant water, draining swamps, and mandatory use of screens or mosquito netting in houses.

Besides legislation, education and propaganda can also be used as weapons in the fight to prevent malaria. A good knowledge of the following topics and issues could be very useful:

- the role of the ecology and of the ability of Anopheles to transmit the disease, and the ways to eradicate the mosquitoes or to prevent their proliferation and contact with man;
- the especially serious threat presented by malaria in children;
- the usefulness of prevention in areas of hypendemic or sporadic malaria.
- the treatment of attacks of fever: the village or community can take responsibility for self-treatment, entrusted to one of its members. This will shorten the interval before a treatment is instituted and avoid clogging health centres with simple malarial attacks. Referral must be reserved for patients who show signs of severe attacks which the community officer must be able to recognize.

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BIBLIOGRAPHY


MALARIA


BERTRAND L. & KLYNENS J. (1903), La lutte contre la _malaria_, Antwerp, 123 p.


JANSSENS P., VERSTRAETE N. & SIENIAWSKI J. (1950), Essais de chimio prophylaxie antipaludique collec-


LEPLAE E. (1931), La culture des quinuquines (note complémentaire), − IRCB Bull., 2, pp. 305-306.


TROPICAL DISEASES


REZETTE J. (1953) Lutte antipaludique, Rapport FOREAMI.


SCHWETZ J. (1927), L’aspect entomologique de la lutte contre la malaria à Elisabethville, – Bruxelles Méd., 42, pp. 1333-1339.


SCHWETZ J. (1940), Sur le paludisme dans l’agglomération de Rutshuru et dans quelques autres localités de ce territoire, – IRCB Bull., 11, pp. 394-417.


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Tropical Diseases


MALARIA


VERHULST G.M.H. & TSHIULA WA TSHIULA (1984), Modèle mathématique pour une étude systématique de la diminution naturelle de la drépanocytose par l’amélioration de l’environnement, - Njorja Méd., 1(8), pp. 28-34.


TROPICAL DISEASES


WHO (1972), International drug monitoring, the role of national centres, meeting report, WHO, Geneva.


WHO (1988), Bench aids for the diagnosis of malaria, Geneva, WHO.


WHO (1990), Model prescribing: Drugs used in parasitic Diseases, WHO, Geneva, 126 p.
LICHERI A. (1928), Considérations sur la malaria au Congo, 6 p.
MASSEY A.Y. (1913), Quelques réflexions sur les maladies tropicales suivantes: la fièvre bileuse hémoglobinurique, la tick fever, l’éléphantiasis, 11 p.
SARCINEU LA (1926), La fièvre bileuse hémoglobinurique dans la région de la Lulunga et ses rapports avec la quinine et la malaria, 37 p.
SCHLESER E. (1946), La lutte antimalariique à Matadi de 1939 à 1945, 30 p.
THEMELIN R. (1930), Un cas d’intoxication par la quinine, 2 p.
VALCZE G. (1922), Prophylaxie antimalariique, 31 p.
VAN DROOGENBROECK J. (1957), A propos de l’oxygénothérapie dans la brusse congolaise et de sa signification dans le traitement de la malaria pernicieuse, 35 p.
ZANETTI V. (1931), Note préliminaire sur la lutte antimalaria et antimoustique à Léopoldville, 15 p.

SPECIAL DOCTORATE
MUYULU PAKASA (1985), Studies on immune complex glomerulonephritis in experimental malaria, Louvain.

SPECIALTY THESIS, UNIVERSITY OF KINSHASA
BADIBANGA BUANGA (1977), Contribution à l’étude du neuropaludisme chez l’enfant zaïrois. A propos de 121 cas, Kinshasa, Pediatric Department.