MALARIA DURING THE LAST DECADE[1]

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The starting point of this paper is rather arbitrarily set at January, 1942, but the selection of this date also has some significance in the knowledge of malaria. Much of the world had just become involved in a great war and was being confronted with problems in disease control relative to the military. Of these diseases by far the most important was malaria.

The following is concerned mainly with human malaria and is not intended to be a comprehensive review of the field but rather of those developments which appear to me to be significant.

Of the tremendous amount of work that has gone on in the malaria of lower animals, reference will be made only to such as is particularly relevant to human malaria or that which can serve for comparison to point up the particular discussion at hand.

BIOLOGY

During this period little attention was paid to the cytology of the parasite. However, MacDougall (1947), studying *Plasmodium vivax* and *P. falciparum* and working specifically with gamete formation definitely established that chromosomes were present in plasmodial parasites. Such had been indicated before but this was the first definitive proof. Additional work by Wolcott (unpublished) indicates that the asexual stages of *P. vivax* have two chromosomes.

There have been no new species of human malaria parasites accepted during this period. Surveys and studies of infected military personnel have delineated more clearly the distribution of the recognized four species of malaria on a world-wide basis and have shown that many strains, particularly of *P. vivax*, exist.

Of particular importance was the discovery of *P. berghei* by Vinche and Lips (1948) in a Congo tree rat. This parasite readily infects other common laboratory animals and for the first time afforded a mammalian parasite that could be easily handled experimentally.

Fairley (1945, 1947) by transfusion showed that blood is noninfective most of the period between the mosquito bites and the primary attacks in *P. vivax* and *P. falciparum*, and during the latent periods between *P. vivax* relapses. On the basis of these observations Fairley postulated that the sporozoites after injection by the mosquito entered some of the organs of the body where they underwent an exo-erythrocytic schizogony which gave rise later to parasites which would invade the blood stream. He further surmised that following the primary attack these exo-erythrocytic bodies did not persist in these organs in the case of *P.*

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falciparum but they did live for a considerable length of time in the case of *P. vivax*, periodically giving off forms which would re-invade the blood and cause parasitic and clinical relapses.

In 1948, Shortt, Garnham and Malamos found pre-erythrocytic schizonts of *P. cynomolgi* in the liver of a monkey. Shortly after that Shortt, Garnham, Covell and Shute (1948) described similar stages of *P. vivax* in the parenchyma cells of the human liver. The next year Shortt *et al.* found a similar but slightly larger preerythrocytic stage of *P. falciparum* also in the liver of man. The first confirmation of the finding of the exo-erythrocytic stages of human malaria is being reported by American workers this year (Jeffery, Wolcott, Young and Williams, 1952). The youngest stage of this cycle so far found is probably three days old. What development occurs between the injection of the sporozoites and the three-day-old forms found in the parenchyma cells of the liver is not yet known.

The finding by Shortt and Garnham (1948) of exo-erythrocytic schizonts of *P. cynomolgi* in the liver of the monkey three and a half months after a sporozoite-induced infection supports the theory that it is from these exo-erythrocytic bodies that parasitic relapses occur in the *vivax* type malaria. Much work remains to be done on the tissue phases of human malaria. So far these bodies have not been described for *P. malariae* or *P. ovale*. It would be particularly interesting to see if the exo-erythrocytic bodies develop in any organ other than the liver. Especially fascinating is the possibility of developmental forms of *P. falciparum* occurring in the brain. The maintenance in tissue culture of cells which would support the growth of exo-erythrocytic bodies of human malaria might elucidate some of these problems and also serve as a test medium for new and promising drugs before actual testing in man began. It would be particularly interesting to know if the plasmodia of lower animals injected into human beings might develop into exo-erythrocytic bodies.

A considerable amount of information has been established on the periodic phenomena of malaria parasites. It has been known for some time that certain strains of *vivax* malaria tended to relapse after long periods of latency. Fairley (1945, 1947) established that a New Guinea strain of malaria did not have long periods of latency after treatment but tended to relapse at frequent intervals. Another strain from New Guinea (the Chesson strain) and an American strain of *vivax* malaria, the St. Elizabeth, were widely used in the search for new drugs by the Americans and were also the subject of an intensive study in prisoner volunteers. In summarizing the life patterns of these two strains Coatney and Cooper (1948) brought out that the outstanding difference was the occurrence in the temperate zone *vivax* of a long latent period between the primary attack and the first relapse. Other work indicates that the tropical strains are more virulent (Young, Eyles and Burgess, 1948). Both types of malaria tend to run their course in the body in about fifteen or eighteen months after a single inoculation.

Cooper *et al.* (1950) also demonstrated that when two different strains of *vivax* malaria, namely the Chesson and the St. Elizabeth, were inoculated into a patient, each ran its particular course in the patient without regard to the other. Information is still needed on the actions of multiple strains in the host, as experience from World War II indicated that some of the returned veterans

were still relapsing up to thirty months after having the first attacks of malaria, whereas the experimental work with a single inoculation indicated that very few *vivax* infections will exist in the body beyond eighteen months.

It was also shown that in *P. falciparum* infections which had been inadequately treated or not treated, parasitemias would exist for an average of 222 days ±25 but that some infections might exist in the body for as long as 480 days (Eyles and Young, 1951). This helps to explain the overwintering of *falciparum* infections in certain temperate zone areas.

In contrast to *vivax* and *falciparum*, a report (Spitler, 1948) during this period indicated that *P. malariae* could exist for as long as 36 years in a latent condition in the body and then become clinically active.

Other periodic phenomena concerned the length of the asexual cycle in *P. vivax*. In the Columbia, South Carolina, laboratory many domestic and foreign strains of malaria have been studied by inducing these infections in neurosyphilitic patients. No strain exhibited a 48-hour periodicity in the asexual cycle (Young, 1944; Young, Ellis and Stubbs, 1947). The periodicities were found to range from 43 to 45 hours in length in a tertian infection.

IMMUNOLOGY

As a result of the study of a large number of strains from various temperate and tropical sources, it is becoming increasingly evident that immunity is not only species specific but is often strain specific in *vivax* malaria (Young, Ellis and Stubbs, 1947; Whorton *et al.*, 1947; Kaplan *et al.*, 1946). *P. falciparum* may exhibit more cross-immunity between strains than *P. vivax* (Boyd *et al.*, 1945). There can be a fairly solid immunity of a homologous type produced by a strain of malaria, particularly if the infection runs a long primary course. This immunity weakens progressively, starting four or five years after the primary infection.

An unsuccessful attempt was made by Heidelberger *et al.* (1946) to produce acquired immunity in man by the multiple injections of a vaccine made from enormous numbers of killed erythrocytic parasites of malaria. It was not successful either in preventing an infection when challenged by sporozoites inoculated by mosquito bites or in modifying the resultant infection.

For the first time there has been demonstrated a possible reservoir host for human malaria. Rodhain in 1948 has shown that *P. malariae* can be transmitted from man to chimpanzee and back to man again. This indicates that in areas such as Africa where man and chimpanzees live in close contact with the vector mosquitoes one might serve as a reservoir for the other.

CULTURE OF MALARIA PARASITES

Great strides have been made in the maintenance and growth of nonhuman plasmodia by various methods. Chicken embryos proved to be an excellent medium for growing many of the avian parasites and as a result much information was obtained on the behavior of plasmodia under such conditions. So far there are no reports of the growth of human plasmodia in chick embryos.

The growth of plasmodia in cultures of various tissues is a significant advance-

ment. An excellent review of this was made recently by Hawking (1951). One of the most important developments was the report of Dubin, Laird and Drinnon (1949, 1950) that the sporozoites of *P. gallinaceum* from mosquitoes' salivary glands could develop into cryptozoites in tissue cultures of normal chicken macrophages. After being grown in this medium for several days the parasites were infective to chicks. However, attempts by these same workers to obtain development of *P. vivax* in tissue cultures of human liver and bone marrow were unsuccessful. An exciting development was the demonstration by McGhee (1949 and 1951) that the avian malaria parasite, *P. lophurae*, can penetrate mouse erythrocytes and could be adapted to a continuous existence in mice.

Attempts to grow the erythrocytic forms of mammalian parasites *in vitro* have been successful by the Harvard University group (Geiman, 1948 and 1951). Species of avian and monkey malaria and apparently *P. vivax* and *P. falciparum* grew with varying success in a very complex medium. Trager (1950) has reported growth of *P. lophurae* for several days extracellularly in a complex medium.

During this period considerable knowledge has been gained of the metabolism and physiology of the nonhuman parasites (Maegraith, 1951; Fulton, 1951) and some information on the human parasites (McKee, 1951). The development of the different cultural techniques indicated above gives hope that in the future information in these fields may be obtained on a more exact basis for the human malaria parasites.

DIAGNOSIS OF MALARIA

There was little change in the methods of diagnosis of malaria during this period. Because of the number of people involved in diagnosing malaria as a result of the war effort, there was an extension and general wide-spread acceptance of the thick film technique. In 1948 Brooke and Donaldson showed that when large groups of blood films were stained in a common container there might be a transfer of parasites from one slide to the other. This, of course, could have a serious effect upon the reported incidence of infection. However, a method was worked out to exclude this possibility (Donaldson and Brooke, 1950) by the addition to the staining solution of a surface active agent, Triton X-30, which not only prevented the transfer of parasites but resulted in cleaner smears with less precipitated stain, bacteria and debris than were obtained by the older methods.

Using a *P. knowlesi* antigen, a complement fixation test was devised which was most useful during the latent period, during which continued positives were indicative of relapses (Dulaney and Watson, 1945).

MALARIA VECTORS

A great deal of specific information about principal vectors of malaria in certain areas was obtained during the war years because of the need of the military for this knowledge in order to control malaria. Important malaria vectors were investigated in other areas, particularly in Africa, Australia and South America. A useful summary of these was made by W. H. W. Komp (1948).

In addition to the increase in information showing the most efficient vector-

parasite relationship in many areas of the world, the transportation of infected troops between malarious areas also afforded the opportunity for studying the ability of known indigenous vectors to become infected with nonindigenous plasmodia. The need for this information was important to the countries concerned because it was necessary to know whether the new relationship would be more or less efficient than the one which already existed. A great deal of this work was summarized by Young (1948). In general it appears that exotic strains of *P. vivax* malaria from various parts of the world demonstrate a high infectivity to certain important anopheline vectors in the areas tried. The principal exception to this was *Anopheles albimanus* from the United States and Carribean areas which did not show this high susceptibility. *P. falciparum* exhibited a much more variable infectivity to important malaria vectors and in general appeared to have a more selective vector-parasite adaptation. Continuing work along this line is showing that strains of *A. albimanus* obtained from areas only a few hundreds of miles apart vary widely in their susceptibility to a single strain of *P. falciparum*. Such strain specificity in the vector-parasite relationship has been demonstrated in several areas of the world.

Observations which might throw some light on the character of the susceptibility of mosquitoes to malaria were made by Burgess in 1948 when he reported the experimental hybridization of *A. quadrimaculatus* amd *A. maculipennis freeborni*, which are the two most important known malaria vectors in the United States. The confirmation of this hybridization was reported by Rozeboom (1952), who also reported the crossing of *A. quadrimaculatus* and *A. aztecus* and of *A. aztecus* and *A. freeborni*. Maryon, Lee and Shute (1951) experimentally crossed *A. maculipennis* var. *atroparvus* and *A. quadrimaculatus*. More recently Burgess (unpublished) obtained hybridization between *A. freeborni* and *A. punctipennis*, two mosquitoes which are not so closely related taxonomically as the above crosses.

So far such experimental crosses have not resulted in the production of a hybrid adult colony which could be tested for its susceptibility to malaria but if and when such is accomplished it should throw much light on the inheritance of malaria susceptibility and perhaps on the mechanism of such susceptibility.

CHEMOTHERAPY

Born of necessity at the beginning of World War II because of the loss of the source of quinine, the program of the developmental chemotherapy in malaria provided one of the most brilliant chapters ever written in the history of this disease. The Allied Forces were to develop within the next ten years compounds far better than quinine which had held undisputed reign for some 300 years. The details of these developments are so tremendous that it would take a long time just to list the various important points in this saga. Therefore this present report will not attempt to indulge in many detailed references but refers the reader to several excellent reviews and evaluations which are now in the literature as follows: Cooper (1949); Coatney (1951); Davey (1951); Finlay (1951); and others.

Among the first important developments was the finding by Shannon *et al.*

(1944) that quinacrine (atabrine), which had been used with equivocal results up until that time, tended to localize in the body tissues and that the effectiveness of this drug was related to the plasma concentration. With this lead they recommended a loading dose of the drug on the first day to saturate the tissues, which was then followed by daily maintenance doses. This regimen produced clinical results which were equivalent to or better than those which had been produced by quinine. Because the plasma drug level dropped slowly there was enough of the drug left in the plasma for a long period of time to eliminate parasites so that the actual effect was a reduction in the frequency of relapses. This plan of a loading dose on the first day also proved to be useful with other drugs.

Shortly after this the reports of the British began to appear which showed that they had developed a good drug named chlorguanide (Paludrine) (Curd, Davey and Rose, 1945). Not only was this drug effective against clinical malaria but it was claimed to be a causal prophylactic of *P. falciparum* (Fairley, 1946).

In the meantime the Americans had embarked on a tremendous drug testing program which eventually was to result in the testing of over 15,000 compounds, some of the details of which can be found in the compilation of Wiselogle (1946). One of the first tangible results of this program was the exploitation of a 4-aminoquinoline drug called chloroquine. This compound was synthesized by the Germans before the war and was called resochin. After exhaustive tests it was discovered that chloroquine was a very efficient parasiticidal drug and that a three-day treatment with this drug was at least equivalent to, if not better than, the ten-day treatment with quinacrine or the longer treatment with quinine. However, it remained more expensive than the British counterpart, Paludrine, so that on a world-wide basis the latter drug became more widely used.

Compounds closely related to chloroquine, namely camoquin, sontochin and oxychloroquin, also appear to be good antimalarial drugs, but apparently not superior to chloroquine, although having similar types of action. Of these, camoquin has probably been the most widely tested but, because of lack of extensive field trials, cannot be said to be any better than chloroquine (Coatney, 1951). It has also been shown that chloroquine and camoquin are effective against clinical attacks when given parenterally.

None of these drugs could radically cure the relapsing *vivax* infections so that attention was once again turned to a different type of compound, the 8-aminoquinoline group. It was remembered that pamaquine (plasmochin) had the ability radically to cure infections but that it was toxic in many cases. Therefore, analogs were developed which were called pentaquine, iso-pentaquine and finally primaquine. They were less toxic, especially primaquine, than plasmochin and each retained the ability radically to cure *vivax* malaria (Alving *et al.*, 1948; Edgcomb *et al.*, 1950).

Recently the large scale treatment of returning troops with Korean malaria dramatically demonstrated the effectiveness of primaquine (Alving *et al.*, 1952; Garrison *et al.*, 1952; Clayman *et al.*, 1952; Hockwald *et al.*, 1952). You have heard today some of the excellent results obtained with primaquine against both the tropical zone *vivax* malaria (Chesson strain) and against the temperate zone

vivax (Korean strain). It appears that at last a drug has been found which will cure relapsing *vivax* malaria at dosages which in most cases do not cause toxic symptoms. While primaquine is a curative drug in that it apparently attacks the exo-erythrocytic stages, it is not a good therapeutic agent and is not the drug of choice to alleviate clinical attacks.

More recently another drug given the name pyrimethamine (Daraprim), one of the 2:4-diaminopyrimidines, was synthesized by Dr. George Hitchings (1952). This drug is currently being subjected to intensive experimental and field trials and shows an amazingly effective action against human malaria parasites. Some of these results you heard this morning. A symposium on Daraprim, published in the Transactions of the Royal Society of Tropical Medicine and Hygiene, September, 1952, brought out much fundamental information on this drug and the results being obtained (Hitchings, 1952; Rollo, 1952; Goodwin, 1952; and Coatney *et al.*, 1952). Schmidt (personal communication, 1952) demonstrated toxic reactions in monkeys receiving this drug in daily doses of 2.5 mgm. per kg. and greater. However, in the amounts given to man for the treatment of malaria (25 mgm. in all) it does not appear to be toxic (Coatney, personal communication, 1952). More evidence is needed on this point.

It has been demonstrated recently that drug resistance can develop to some of the newer antimalarials. Bishop (1951) has reviewed the development of drug resistance in avian, monkey, and human malaria. Experimental and field reports indicate that *vivax*, *falciparum* and *quartan* malaria are developing resistance to chlorguanide. Experimental work with the nonhuman malarias and some of the field reports in human malarias indicate definitely that this resistance is retained after passage through mosquitoes. Bishop and McConnachie (1952) showed that one of the 8-aminoquinolines, pamaquine, could produce drug resistance in *P. gallinaceum*. It remains to be seen whether the other 8-aminoquinolines, including primaquine, will have this disadvantageous effect.

Coatney and his co-workers (personal communication, 1952) have definitely shown that drug resistance can be produced in *vivax* malaria against Daraprim, using very small doses, and that this resistance persisted after being transmitted by mosquitoes. We await with interest reports from large scale trials to find out if drug resistance will develop to Daraprim after therapeutic doses but, in view of experience with chlorguanide in the field, one cannot be too optimistic.

So far there has been no significant resistance developed to quinine, quinacrine, or chloroquine in human malaria (Bishop, 1951). Chloroquine still seems to act normally against the Chesson strain of *vivax* after it had developed a thousand-times resistance to chlorguanide (Cooper, Coatney and Imboden, 1950). As Bishop (1951) so cogently indicates, in searching for new compounds for the treatment of malaria the factor of resistance also must be included in the assessment. Another interesting and significant development in drug resistance is that the resistance to a certain drug might in some cases be carried over as resistance to other drugs but not necessarily to all of the antimalarial drugs. The presence or absence of such cross resistance in the malarial drugs is in need of exploration.

MALARIA CONTROL

Another brilliant achievement has been the tremendous progress in malaria control. In 1942 the principles of mosquito control were to control the breeding water by draining or fluctuation, the killing of larvae by using oil sprays or Paris green, the killing of adults by space sprays of pyrethrins, and the protection of personnel by the screening of houses, the use of bed-nets, etc.

A synthetic compound, dichloro-diphenyl-trichlorethane, to become known as DDT, had been shown only recently to have insecticidal properties. American tests on DDT started in 1942. It was soon discovered to be a good mosquito larvicide (Deonier *et al.*, 1945a and b) and also that when applied as a residual spray in buildings it retained its ability to kill adult mosquitoes for a long period of time (Gahan and Lindquist, 1945; Gahan *et al.*, 1945a, 1945b).

This opened a new era in the control of malaria and rapid advances were made, particularly in the use of this chemical as a residual toxicant. By such application the malaria chain was broken at one of its weakest links, that is, the vector was attacked at the time it acquired the plasmodium from the human host. In rapid succession followed other useful developments of DDT such as spraying from planes and the production of fogs, all of which had their special applications against larvae or adult mosquitoes. Furthermore, other chlorinated hydrocarbon analogs such as BHC (benzene hexachloride), chlordan, toxaphene, DDD, methoxychlor, heptachlor, aldrin, and dieldrin were developed, which varied in their effectiveness but all of which showed some ability to kill mosquitoes.

In addition, there were developed other new insecticides containing phosphorus such as parathion, HETP (hexaethyltetraphosphate), and TEPP (tetraethyl-pyrophosphate). All of these are very toxic to insects but unfortunately also have a high toxicity to mammals, which restricts their usage. Recently a synthetic substance similar to pyrethrin (allethrin) has been produced.

Space sprays proved to be of value and became widely used following the development of methods of putting pyrethrins in a liquefied gas which when released produced an aerosol. Later DDT was combined with the pyrethrins to increase the effectiveness of the sprays.

The details of the developments of the above methods can be found in many publications, particularly Boyd's "Malariology" (1949), Russell's "Malaria" (1952), and a review by Symes (1951).

After several years of experience in the use of insecticides it became obvious that flies and then pest culicine mosquitoes were becoming resistant to DDT and other chlorinated hydrocarbon insecticides. This development boded ill for those controlling the anopheline mosquitoes and for several years, although carefully watched for, no report of such resistance occurred. Unfortunately, however, there is now a report from the Tennessee Valley Authority (Krusé, Hawkins and Ludvik, 1952) which shows that airplane spray tests with DDT have shown a ten to twenty-five fold increase in the LD-50 values for insectary-reared fourth instar *A. quadrimaculatus* larvae and that this has occurred since 1949. The mean amount of DDT required to give one hundred per cent kill of fourth stage instar larvae has increased about twenty times during 1950 and 1951 as compared with the period 1946–1949. Field tests indicate that in a natural population in 1951

it was necessary to double the rate of application of DDT distributed by plane in order to obtain results as satisfactory as those experienced during previous years.

Control programs now are based on the use of some of the above insecticides, but in most cases the technic of residual spray is used. This type of control has been found to be feasible in many countries because of its relatively low cost. Pampana (1951), in discussing the major campaigns of malaria control with residual sprays, listed the countries with national schemes of such control as follows: AFRICA, Transvaal, Madagascar, Mauritius, South Rhodesia; ASIA, Ceylon, some parts of India, Afghanistan, Indonesia, Thailand, Viet Nam; EUROPE, Greece, Italy, Portugal, Yugoslavia; the AMERICAS, Argentina, Bolivia, Brazil, Eduador, U.S.A., British Guiana, Mexico, Peru, Venezuela.

INCIDENCE

The story of the incidence of malaria in the United States is well known to this group and is simply that the amount of natural malaria has been declining gradually for many years. This decline was interrupted for a brief period about 1945 and on a lesser scale in 1951–1952 by the return of many troops infected with foreign relapsing malaria. This interruption was only temporary and now it is confidently expected that malaria will be eradicated as a disease in this country. The evanescence of malaria as a major health problem in the U.S.A. was dramatized last year by the National Malaria Society's dissolving itself (Am. J. Trop. Med. Hyg. **1:** 526–528, 1952). Certainly this is one of the few times in medical history that a society has voluntarily ceased to exist because its aims had been fulfilled.

The incidence of malaria seems to be declining on a world-wide basis. Due to the exigencies of war and to the return of infected troops, some countries in temperate zones experienced a temporary outbreak of malaria during and after World War II. However, the wide-scale use of control programs is having a telling effect upon the incidence of the disease. Pampana (1951) estimates that the residual spray program alone is eliminating malaria which affected 480,000,000 people. He says that it has ceased to be a public health problem in many places where it was mainly a disease of rural districts. There are many publications in the world literature on the reduction of malaria in areas where national control schemes are under way (Russell, 1952). The outlook for the continuation of the reduction in the incidence of malaria seems to be very good. Even so it is still a world-wide public health problem of enormous magnitude. Just recently Russell (1952) estimated that fifteen per cent of the world's population suffer from malaria annually.

METHODOLOGY

It seems to me that certain concepts which were developed during the past ten years and which resulted in some of the advances already catalogued have a definite place in this review picture.

In the field of chemotherapy the development of a program of drug screening that allowed for the testing of over 15,000 compounds by the American workers is noteworthy. The antimalarial activity of compounds was tested mainly against

avian malarias and to a lesser extent against the simian malarias. The large scale use of volunteers of both army personnel and prison inmates enabled the final assessment of the drugs which had shown promise in the screening tests.

Paralleling this was a similar development in the large scale rearing of anopheline mosquitoes and the development of technics for the mass feeding of suspected and known vectors upon malarious patients. This enabled the rapid assessment of the ability of various vectors to transmit different species of malaria often introduced. Equally important, it made possible a reliable method for furnishing large numbers of infected mosquitoes to carry on the drug testing program in prisoners and in army volunteers.

Also important was the tremendous advance in the methodology of the testing and evaluation of potential insecticides.

It is obvious that the above methodologies have implications of tremendous importance in fields other than malaria to which they have been or can be applied.

PROSPECT

The advances in malariology have been greater perhaps during the past ten years than during any other similar length of time. There can be no gainsaying the fact that more people have been protected against the disease than in any decade.

However, it must be admitted that all of the knowledge gained cannot be regarded as net profit. The ability of some of the anti-malarials to induce resistance in the parasites and of the insecticides to produce resistant strains of mosquitoes is an indication that our practical knowledge far exceeds our basic knowledge of this disease complex. One might envision momentarily the prospect of a drug-resistant plasmodium being transmitted by an insecticide-resistant vector. Our hope is that the accumulation of new knowledge will outrun the development of these adverse conditions. These considerations do, however, underwrite the necessity of continuing fundamental research into this disease.

The progress in malaria has been so great in the past ten years that it has been possible to express for the first time, as did the third session of the Expert Committee on Malaria (1950), that the ultimate aim of the World Health Organization could be to eliminate this disease as a public health problem from the world. Let us hope, and the prospect is heartening, that by the end of another decade malaria will have lost its designation as the most important human disease and will be of only minor importance. If the progress of the last ten years can be repeated the chances of achieving this seem to be good.

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