

LEAGUE OF NATIONS.

C.H./Malaria/238.

Geneva, May 12th, 1936.

HEALTH ORGANISATION.

MALARIA COMMISSION.

The Secretary of the Malaria Commission has the honour to communicate herewith an article by Professor G. BASTIANELLI on the respective rôles of immunity and treatment in the cure of malaria.

THE TREATMENT OF MALARIA.

Immunity and Therapeutics.

In an article entitled "Notes on the Treatment of Malaria" published in "Forze Sanitarie" in January 1933, after summarising the known facts concerning the natural course of the disease when untreated*, I dealt with the evolution of falciparum infection and the course taken by recrudescences in treated patients, and showed that quinine does not sterilise and does not definitely cure. My conclusion was therefore that "the disease dies away in man through a spontaneous process which may be described as immunizatory. Quinine hides the disease, terminates the attacks, and protects the patient; given at the proper time, it prevents relapses and enables the individual to go about his business; and all the time that these benefits are being conferred the disease is being cured by the above-mentioned process, which is facilitated by the action of the drug."

I submit a few considerations, mainly of a clinical nature, which seem to me to prove with sufficient certitude that present-day therapeutic methods do not interfere with the immunisation processes which lead to the final cure. My aim in so doing is to establish certain principles - principles, and not methods or systems - of treatment.

* Previously to the employment of cinchona, a Roman doctor, LANCISI, described the natural course of the serious malarial fevers which we now call aestivo-autumnal, and noted that they gradually diminished until a spontaneous cure occurred in winter. In the English edition of the book by MARCHIAFAVA and BIGNAMI (1900), a chapter is devoted to the spontaneous cure "which may be observed not only in benign fevers," but also in fevers of the aestivo-autumnal group. LANCISI's quotation is from the second Italian edition of the treatise by MARCHIAFAVA, BIGNAMI and NAZARI.

The above concept of the manner in which the final cure of treated infection occurs is based on clinical observations. It coincides with what seems to follow from recent studies of the action of chemo-therapeutic substances on protozoic diseases. The researches of JANCSÓ, and of SINGER and FISHER, into the fixation of fluorescent chemotherapeutic substances on the body of the parasite, are well known. In a short survey of the action of chemotherapeutic substances on spirochaete and protozoon infections, SINGER * (1935) concludes that the acute chemotherapeutical effect consisting in the rapid disappearance of the parasites is only part of the curative process. Immunisation processes are absolutely necessary to ensure a final cure of a spirochaete or protozoon infection; the direct effect of the chemotherapeutic agent cannot in itself produce a cure. The manner in which a cure is effected by a given medicament is as follows: the substance becomes incorporated in the parasite, and there undergoes changes during which the parasitic cell dies. The virulence of any parasites that make their appearance in the organism, and they are finally killed.

Whether there exists any relationship between chemotherapeutic action and the appearance of these forces tending towards immunisation and, more generally, towards complete cure, is another question.

During the last few years, certain views have been framed regarding the treatment of malaria that are based on our latest knowledge of immunisation (or premunition) and of the various strains of the same parasite species. These ideas have led to the conception of - and later to proposals for - certain curative methods based mainly on the view that early treatment retards the advent of that immunity which is curative of active infection in the individual; that therefore it is preferable to refrain from applying treatment too early, and to leave the patient - naturally within certain limits and for a certain time - without treatment, so as to enable him to acquire a curative immunity. It has even been suggested that, in hyperendemic zones where reinfections are the rule, any attempt to effect a permanent cure must be futile and may lead to undesirable results by preventing the acquisition of that immunity which, to a certain extent, reduces the severity of reinfections. Further on I shall analyse these opinions in greater detail.

If we take first the aestivo-autumnal fevers, the clinical study of malaria shows that in fresh subjects who, after once being infected, are not again exposed to infection, the disease gradually diminishes in severity until it disappears.

This gradual diminution of severity is proved by :

- (a) the increasingly long intervals between relapses;
- (b) the diminished severity of relapses as compared with the first attack, whatever treatment may then have been applied; and
- (c) the fact that they yield more readily to treatment.

* E. SINGER. Die Wirkungsweise der Chemotherapeutica bei Spirochäten und Protozoeninfektionen. Medizinische Klinik, 1935, No. 12. The opinion of the authors is that the fixation of a remedy on the body of the parasite is an indispensable preliminary condition to chemotherapeutic action, but is not the same thing as that action. Inactive remedies may be incorporated by the parasites, but there is no known case of a substance that has not been incorporated by the parasites having produced any therapeutic effect. The substance does not produce its effect in its original state, but after the changes it undergoes in the body of the parasite. Action *in vivo* and action *in vitro* are two quite separate things.

This decrease of severity is observed both in treated cases and in cases which have been left to themselves, though in the latter it follows a different course (see Forze Sanitarie). After a number of relapses (and on very rare occasions, in Italy, without any relapse), the final cure takes place. The time which elapses before complete cure varies to a very remarkable extent, both in treated and non-treated cases. The experience of ancient Rome proved that the disease contracted between July and the end of late autumn, dies out in the spring. Obviously dwellers in the country were exposed to reinfection. In 1899 BASTIANELLI and BIGNAMI*, when making a careful study of the epidemiology of these fevers in a small community (Ostia, with a population of about 200 persons almost all infected), found no gametocyte (crescent) carriers in May and June. They examined all the patients who came to the Santo Spirito hospital during those two months, and found only four gametocyte-carriers among about seventy persons suffering from tertian or quartan malaria. In July the fresh infections began on these data, taking into account the possibility of reinfections, we can calculate that the maximum total period of falciparum infection does not exceed eight or nine months.

Experimentally induced malaria (JAMES, 1932)** has supplied more definite data i.e. that the minimum period is a few weeks and the maximum eight months. Some of JAMES's patients recovered spontaneously, and some (although treated) were successfully reinfected three or four months later. In about five months' time they appeared to have become incapable of reinfection. LEGA has reported some cases of malignant tertian treated with atebirin and quinine, the patients not being exposed to reinfection. The total duration of the disease (the cases in question were kept under observation for a further year) was six, eight and nine months. Relapses were rare, only about two in each case, occurring at considerable intervals; even at an interval of three or four months. Only in one case did the last relapse occur during the tenth month from the onset of the disease. In all the other cases, the last relapse occurred within a maximum period of eight or nine months.

It is not an easy matter to institute any comparison between the duration of the disease in treated and untreated cases. Cases of infection by falciparum that have been left untreated for a considerable number of months are too rarely met with. I have seldom met a case which has remained for a longer period without treatment than the one I referred to in the aforesaid article in 1933. The strain was Sardinian, and the patient had been suffering for four months and fifteen days when he arrived in Rome and the disease was diagnosed and treated.

* BASTIANELLI G. and BIGNAMI A., La malaria e le zanzare. Paper read at the Congress of the Società Italiana di Medicina interna, 1899.

** JAMES, NICHOL, SHUTE. A study of induced malignant tertian Malaria. Proceedings of the Royal Society of Medicine, vol. XXV, 1932.

The curve showed a typical decline in the infection, which probably, left to itself, would have continued for some time more.* The cases quoted by JAMES only remained for a very short time without treatment.

The few observed cases of untreated persons suffering from malaria suffice to prove that in these cases the progress of the disease is as varied as in treated cases. I am afraid that criticism of early treatment on the ground that it prevents the acquisition of immunising forces, and that thus the malady may be prolonged, are based rather on an a priori concept than on observation. Early-treated patients are not more liable to relapses than cases that have received tardier treatment, unless treatment was begun at so late a stage that the patient had already, without any outside help, made considerable progress towards immunity.

A patient who has been efficiently treated (observation 20, Appendix, JAMES, loc. cit. 1932) may take seven months to cure and may have sixty-nine days of fever. Others, also treated, may get rid of the disease after the first attack (such cases are rare, especially in Italy) or in a few weeks. If, on the other hand, in an untreated individual, four and a half months of active illness do not suffice to bring about a spontaneous cure, this means that the clinical activity of the disease is not helping the patient to acquire protection. These considerations do not help us to solve the problem whether it is better to give treatment as early as possible or to wait (in the case of malignant tertian, this problem does not arise, except under experimental conditions); but simply tend to show that treatment is not responsible for a slow progress in certain treated cases, and also serve as a warning against an opinion which lies behind certain views as to the desirability or otherwise of administering immediate treatment to a patient, (the opinion that a patient promptly treated at the first attack acquires insufficient protection against reinoculation with the same strain). I wish to make it clear that it is not the active illness that favours the acquisition of those forces which eventually lead to a definitive cure. These forces are acquired during the incubation period, during the active period of the disease, and later when, as a result of the remedial treatment, all clinical symptoms have disappeared.

A certain period of time must elapse before these forces can be acquired, and this period varies from patient to patient according to their individual capacity to acquire them. In the case of infection with falciparum, the maximum period is eight to nine months, and within this period all the relapses whether frequent or infrequent occur. When the last relapse takes place, this being sometimes preceded by a long period of absence of symptoms and parasites - (when ordinary tests are applied) - it must be borne in mind that in

* The patient became infected in Sardinia. He had the first attack on September 4th, and was immediately transferred to a clinic in the neighbourhood of Milan, where he was treated until January 20th for undulant fever. This is therefore a case of genuine decline without treatment and without subsequent exposure to reinfection.

the preceding period there have been created, unnoticed, those conditions causing this final manifestation of the disease to be the last chapter of the whole story.

Treatment does not, therefore, interfere with the acquisition of those forces which lead to a final cure, nor does the fact of allowing the disease to follow its own course accelerate their acquisition. These powers are generated in exactly the same way in a patient who has received early and efficacious treatment and in one who has been treated ineffectively at a late stage. But they are acquired in either case in different lapses of time which vary according to the individual disposition of the patient. One necessary condition for their acquisition is time, the maximum limit of which we now know with greater certainty.

Obviously, the defensive reactions of the subject also determine the seriousness of the case. Cases of death from acute malaria are rare, and were rare, as compared with the large number of persons infected with malignant tertian, even in those days when the disease was widespread and severe. Such cases are serious from the first onset, and can hardly ever be cured. These are individuals whose organism has produced no defensive reaction either during the incubation period or subsequently; consequently, the parasite's capacity of reproduction is infinite. The fact that fatal cases of malaria are so rare when the infection is by vivax can have no other explanation.

What is the relations ip between the time factor necessary for a final cure, and resistance to re-infections?

JAMES'S speedily-cured cases became resistant only four or five months from the onset of the disease after two or three inoculations. JAMES'S cases are few in number, but a great deal of information on the subject has been supplied by CIUCA'S experiments, which are summarised in a table (page 153 of the volume), being the result of the study of 544 persons who had been inoculated more than once with malignant tertian.

CIUCA believes that acquired immunity can only be obtained after five to ten successive reinoculations. "This immunity is acquired (in malignant tertian) more slowly, because treatment is most frequently given during the first period of the attack." CIUCA records, in the majority of his cases, only the number of reinoculations. If I understand him aright, he argues that resistance is acquired through the repetition of inoculations. Only in eleven selected cases are the dates of the beginning of the attack and of the reinoculations down to the acquisition of resistance given.

* CIUCA, BALIF, VILRU. Contribution à l'étude de l'infection paludéenne intentionnellement provoquée par inoculation de sang virulent. Published as a tribute to Professor CANTUCUZENE, Masson, 1934.

I quote a few cases.

One with a spontaneous cure of the first attack became resistant after four months; another, treated with plasmoquine, after six months; a third, treated at the first inoculation, after seven months; a fourth, treated at the first positive inoculation, became cured spontaneously five months after the second inoculation and was no longer receptive. In another case, resistance was also acquired after seven months. In one case (No.144) in which the cure was spontaneous, after two years and one month, a second reinoculation was positive. Other cases were still receptive after 5, 9, and 11 months. Another case proved resistant to a second inoculation after eight months, the first infection having been treated with plasmoquine.

These are the only cases in which the dates of the first attack and the reinoculations are given. Perhaps the history of the other cases might provide information which would be useful in the present discussion.

In any case, CIUCA's data concerning the time in which, after various reinoculations, immunity was acquired, partly correspond with the maximum period within which a final cure takes place. Some of his reinoculations which gave a positive reaction after the maximum time-limit were made a very long time (about two years) after the first onset of the disease.

But the question arises whether inoculations of malignant tertian blood having possibly a high parasite count, inoculations which should, in ordinary circumstances, be followed by an immediate outbreak of the disease* without any period of "incubation" or "adaptation", are sufficient tests of resistance. It is not unfair to suppose that this method of attack may disturb an acquired, but unstable, immunising force. It is a known fact that malignant tertian (in contradistinction to benign tertian) inoculated by means of blood takes a course similar, in malignancy and the number of relapses, to that of infection with sporozoa.

I would suggest that in future research work on this subject malignant tertian cases should not be reinoculated before the nine months of the maximum time have elapsed, or at any rate not within five months from the primary attack, and that reinoculations should be made with sporozoa.

From the above observations it seems more likely that the subsequent recurrence of a clinically active disease or the succession of reinoculations is not a factor which increases or accelerates the acquisition of resistance. Possibly it reduces it.

* BASTIANELLI and BIGNAMI. Studi sull'infezione malarica. R. Accademia medica di Roma, 20th year, 1893-94. Inoculating with 2 cc. of malignant tertian blood with a rather high parasite rate, the disease developed after two days; using blood with a moderate parasite rate, the dose being $\frac{3}{4}$ cc., after five days; with $\frac{2}{10}$ cc. using blood with a rather high parasite rate, after four days.

In vivax infections, the progress and duration of the disease until its final cure also vary considerably. When there are relapses, the duration is longer than in the case of infection by falciparum. In this case, the whole course of the disease includes the primary attack with its recrudescences, the latent state, which may last for nine months, and the recurrence with its possible recrudescences. Of these different periods of the disease, the most stable is the "latent period", which lasts eight or nine months; the number of recrudescences, both after the primary onset and after the recurrence, is very variable. How long the disease lasts when untreated from beginning to end has not been very clearly established. Observations in ordinary practice, in cases not exposed to reinfection, are lacking: it has only been possible to gather data in the case of experimentally induced malaria. Reverting to JAMES's cases*, I note two cases in which no treatment was given: in one, the disease lasted for about 11 months, including the primary attack, the latent stage, and the recurrence, after which, not only was the cure complete, but all attempts to reinfect with various series of highly-infected mosquitoes, made one year later, failed. Subsequently, one attempt succeeded with Plasmodium ovale; a little previous to this, an inoculation with falciparum had also succeeded. In another case (also a case of infection by sporozoa), the duration was about 11 months. In this case, during the latent stage, reinoculations with blood and sporozoa gave positive results. In this case too, the disease had followed its course without treatment. After the recurrence, from which a spontaneous recovery was made, repeated attempts to infect with sporozoa also failed. This would seem to prove that only after the recurrence is the disease finally mastered, i.e., curative immunity is acquired, together with immunity against reinfection by the same strain. These two forms of immunity are acquired simultaneously and by the same process.

Patients treated during the primary attack with quinine or atabrin all show the same curve of decline as untreated cases. JAMES's graph (Third Report of the Malaria Commission of the League of Nations) holds good for both. The duration is about twelve months, or slightly more. LEGA has also collected data concerning a few cases met with in private practice, of persons who were not exposed to reinfection, but who carried on their normal life and occupations. In all these cases there was recurrence with its usual recrudescences. A final cure took place in 10, 9 or 13 months in some cases; in others, after more than a year; in three cases, after more than two years. From these few observations we may conclude that treated tertian may last for a longer time than untreated tertian, but observed cases with a longer and natural course - i.e., the course without treatment - are so scarce that no rule can be laid down. What is referred to in the Third Report of the League of Nations as "The Natural Course in Relapsing Cases of Benign Tertian Malaria" is based

* JAMES. Transactions of the Royal Society of Tropical Medicine and Hygiene. From 1925 onwards; see also the discussions of the Royal Society on malaria questions in the following years.

on the Horton experiment - the duration being twelve to thirteen months - in which the patients were treated with quinine after a large number of attacks at the first invasion. After the latent period, many of the patients were not treated, as is often also the case with us, because ordinarily the recrudescences disappear spontaneously. There is thus no difference between cases in which the course was wholly spontaneous and cases treated during the primary attack. According to JAMES, immunity to reinfection occurs when the disease has not been treated: "In our experience, this state of immunity is acquired only when every attack or relapse has been left for some time without quinine"; he then adds that "Such immunity is more noticeable in patients who, after a recurrence, have recovered without treatment".

MOSNA* (1934/35) has succeeded in reinoculating eleven persons cured of benign tertian, one year after the cure: five with the same strain (Madagascar), others with an Italian strain. They had not all had a recurrence. During the primary attack, all were treated with quinine, but not all during the recurrence. The duration of the disease in the longest cases remained within the limits of the ordinary period. MOSNA found that complete or almost complete immunity had been acquired against the same strain, and a certain degree of resistance to other strains. He concludes that quinine treatment does not seem to prevent the development of the immunising process.

It is held (JAMES) that patients who undergo daily chemotherapeutic prophylaxis gain little or no immunity to the disease. In an experiment by JAMES, prophylaxis was carried out for two months from the date of inoculation, but as soon as quinine was stopped, fever developed.

The experimental data are not sufficient to decide this point, for they cover only a short period, or at any rate one which is not sufficiently long. But, in addition to the experimental data, there also exist those acquired by field experience. Field prophylaxis is certainly not so good a foundation for reliable conclusions as experiment. Hence we only take the results of such experience into consideration when they were acquired in special circumstances (i.e., in conditions of serious exposure to infection), when they relate to an exceptional number of persons who were not immune, and when they were noted with an accuracy comparable to that of an experiment.

The experience of the brothers SERGENT during the great war in the Near East was undertaken, as is generally known, under circumstances in which exceptional accuracy was possible. In addition to the salutary action of clinical prophylaxis on the French soldiers, it has shown something more. When the war came to an end, or when the men were on leave, prophylaxis stopped. It was important to ascertain what happened to the repatriated men after the cessation of prophylaxis and of exposure to reinfection. EDMOND SERGENT has been good enough to summarise for me as follows what has

* Rivista di Malariologia, 1935.

been ascertained regarding the men who had returned to France and had practically ceased prophylaxis:

"When the men were sent back to France on leave or permanently, it was no longer possible to arrange for the administration of quinine by N.C.O.'s. Every man was therefore given a stock of quinine, and was told to continue taking it for at least a fortnight. Clearly this advice, which was not supported by any compulsion, was not properly followed. When the repatriated men landed at Marseilles or Toulon, quantities of quinine were found, which they had not taken. I was unable personally to keep the repatriated men under observation, but nowhere have I read or heard that serious attacks were observed after they had stopped taking quinine. On the other hand, a fact which has struck several observers, particularly RIEUX, is that the Macedonians, as they were called, i.e., the soldiers returning from Macedonia, 1) recovered very quickly in their native country; 2) caused no case of contagion."

This experience cannot have the accuracy of a piece of research, but it would be a mistake to undervalue it. In the first place, it is experience on a very wide scale with men who were in the worst condition of exposure to very severe malaria. In cases covering large numbers of patients, and with careful observation, such extensive experience has the value of an experiment. What happened to the men who stopped prophylaxis shows that they had acquired curative immunity - not merely a reduction or temporary absence of clinical symptoms during prophylaxis - and this happened because prophylaxis had been strict and had lasted a long time, probably almost as long a time as is requisite to acquire curative immunity. The chemotherapeutic substance acts, in those undergoing prophylaxis, on the parasite at the moment when it is becoming sensitive to the action of the drug, and reduces its development, thus preventing the clinical manifestations of the disease or materially attenuating their intensity.

In such a clinically latent state, both the parasites and the organism are still at work; thus, even in the absence of clinical manifestations, the immunising powers develop. In judging the degree of immunity acquired by those undergoing prophylaxis, the time factor must be regarded as essential. If, when the disease is left to itself, nine months, one year, or even two (according to the various species of parasite)*, are necessary to acquire curative immunity, it is not to be expected that this will be acquired in a shorter time during prophylaxis. The time factor, as has been made clear by the study of the spontaneous progress of the disease, is of primary importance.

Studies of bird malaria have materially contributed to our knowledge of human malaria. We need only recall McCALLUM's discovery. So far as therapy is concerned, the study of chemotherapeutic substances in birds undertaken by

* These figures refer to infection by falciparum and vivax. Nothing equally certain is known about quartan fever.

ROEHL has made possible the progress achieved with synthetic remedies in the last few years. Certain principles are common to bird malaria and human malaria. Naturally the application to human malaria of the results obtained by the study of bird malaria must be made with caution. But certain principles are generally applicable. Those based on the behaviour of birds towards a superinfection are applicable to man. LOURIE (1934)* has studied how canaries infected with Pl. cathemerium behave towards a superinfection according to whether they are treated with quinine or not. As is well known, when the infection is left to itself, birds which have passed through the crisis and have had slight relapses enter a latent period during which they are in a state of absolute premunition. This is acquired in a few weeks, after which no attempt at superinfection can succeed.

Having determined the non-toxic doses of quinine sufficient to send the primary attack abortive, LOURIE was able to prove that successfully treated birds behaved towards a superinfection in the same way as untreated birds - "employing the term immunity to indicate a function which, in the absence of treatment simultaneously with an infection, would be capable of preventing the accumulation of parasites in the blood; infected birds can, in fact, acquire during a prolonged treatment with quinine an immunity equivalent to that acquired during the same period by untreated birds."

In his treatise LOURIE then goes on to make a few remarks on the differences in the results obtained in birds and those obtained in infection by Plasmodium vivax, but they are of no importance to our present subject.

As regards chemotherapeutic prophylaxis, the author observes that, in experiments with bird malaria, quinine treatment was prolonged beyond the time needed by untreated cases to acquire complete immunity. In experimental human prophylaxis, too short a time was allowed for quinine treatment, and at least ten months would be needed to obtain curative immunity; it is probable that if a patient were subjected to chemotherapeutic prophylaxis for as long as is required to acquire such curative immunity, there would at least be no more clinical phenomena when the remedy ceased to be administered.

LOURIE's researches will certainly make a greater impression than clinical considerations. The latter are always less simple than an experiment; but they point the way to it, and may be sufficient in themselves to yield a conclusion. We need only recall how malaria is cured - that the chemotherapeutic substance causes a cessation of the attacks and masks the disease, while cure is brought about by an immunising process - to reach the conclusion set out in my article of 1933, namely that therapy may possibly hasten, and certain cannot hinder, the acquisition of immunity.

The problem of the immediate or postponed treatment of the primary attack from the point of view of the acquisition of immunity may, as I have stated above, be neglected. But it is important to examine, in the light of the facts set out above, the principle maintained by many well-known modern

* LOURIE, Studies on Chemotherapy in Bird Malaria, Annals of Tropical Medicine and Parasitology, Liverpool, XXVIII, Nos. 3 and following).

malariaologists, which should serve as a guide in the treatment of the inhabitants of districts in which exposure to reinfection is more or less permanent. C. SCHILLING, in the important report submitted to the Volta Congress at Rome in 1933 (autumn), says that it would be most interesting if children in a bad endemic malaria zone could be kept under observation from birth and for years after without being treated; and further on he raises the question whether, if the infections of the inhabitants of a malarial zone or of a sleeping-sickness focus were completely sterilised, we should be conferring an advantage on the population. Might we not be depriving them of the possibility of acquiring immunity? The best solution would be, if possible, to mitigate individual attacks so that they should not injure the growth and general health of the children, while the infection should be given sufficient latitude to reach the state of unstable immunity.

SINTON, in his criticism of the third report of the Malaria Commission of the League, concludes, under the second head, that, among populations exposed to continual infection and reinfection from various strains and species of parasites, such radical treatment (i.e., that advised in the previous paragraph for populations in which the chances of reinfection are comparatively slight) should not be attempted, but that treatment should only aim at "producing a rapid cure of the attacks". It is unnecessary to go into the long discussion that precedes this conclusion; but the dominant idea both of SINTON and of the report criticised by him is that no treatment or plan of treatment should interfere unduly with the processes of immunisation, which is so advantageous to populations after infancy. It is not very easy to reconcile this idea with the assertion that a clinical prophylaxis, "which is, in fact, an early clinical curative treatment", may help the individual (and here I agree with SINTON) to acquire a considerable degree of immunity.

The main reason for which there need be no apprehension of injury's being caused by radical treatment is that no treatment, even the most effective, is ever radical. A treatment can only be absolutely radical at a stage of the disease when the latter has reached the end of its proper course. The new synthetic remedies used, either alone or in combination, have reduced the frequency of relapses, but so far a "sterilisation magna" does not exist.* The patient whose primary attack has been cured, even if he has no more clinical relapses, still retains the parasites, even when none can be detected on examination. A relapse may be expected at any moment within the maximum period. While the disease is spontaneously latent, or is kept under by the remedies, reactions leading to immunity are continually taking place in the organism. The patient undergoing treatment acquires immunity in the same way as the patient left to himself, but without disturbance or suffering; his clinical manifestations are in posse. There is no analogy to justify the opinion that the disease whether in a more or less active form can more readily confer immunity than the latent infection which works in silence. The contrary

* It is possible that later experience may show that the ~~continued~~ ^{continued} use of synthetic remedies can attain it. The whole problem will then have to be reconsidered.

may be the case. But, apart from every other consideration, there is no documentary evidence to show that a population with hyperendemic malaria, treated in such a way as to obtain unstable immunity, acquires greater immunity than a population treated according to the principles found to be effective among hospital patients. This is an a priori assumption. If a programme were to be drawn up for a hyperendemic district, it would be to apply the optimum discovered from the most favourable hospital experience. The first part of this programme, apart from chemotherapeutic prophylaxis, would be that of the present international experiment in prophylaxis and therapy with synthetic remedies; but the prophylaxis would have lasted longer. Despite this, appreciable results are already being achieved. But the same experiment also shows how much it costs to carry out such a programme, even in a small community. Hence, unfortunately, the treatment of malaria in poor and very exposed populations will always have to be a compromise. But compromise must not become a principle.

SUMMARY.

The present writer seeks to demonstrate with the help of published clinical and experimental data, that the current treatment of malaria does not interfere with the immunising processes that lead to final cure. He emphasises the time factor necessary for the acquisition of immunity. He examines chemotherapeutic prophylaxis from this point of view. He discusses the view that, in a hyperendemic district, so-called radical treatment may reduce or prevent resistance to reinfection.
