THE PRESENT POSITION OF
THE QUININE PROPHYLAXIS OF MALARIA.

BY
W. CARNEGIE BROWN, M.D.

No fact in tropical sanitation has been more completely established, and none perhaps is of greater moment than that anopheline reduction below fever limit may be effected in places where only a few years ago any attempt to exterminate mosquitoes would have been pronounced futile and hopeless. But it is also true that from physical and economic reasons the repression of malaria by thwarting anopheline transmission is in many places still impracticable; and in such circumstances prophylaxis by reinforcing human resistance necessarily constitutes the principal line of defence. Nay more, the whole trend of recent enquiry and the results of clinical experiment have been to show that at the present day more than ever before, the scientific administration of quinine is established as a measure of very great value, and that it is indispensable in the general prevention of the disease.

As is the case in many other aspects of the malaria problem, there is still, however, considerable diversity of opinion as to the value of quinine prophylaxis, and even as to the correct application of the term. Strictly speaking, quinine prophylaxis may be defined as placing the system in such a condition by the administration of the drug that the development of symptoms after a first or fresh infection is inhibited; but in practice no such limit is placed on the meaning, and the term is generally applied to the prevention of relapses (in which the action of quinine is more or less curative) and also to the improvement in the health of a community which follows the quininisation of infected individuals, where it acts by removing the source of contagion.

Professional estimation of the value of quinine prophylaxis has varied greatly since the days, long before the discovery of the parasite, when the drug was first used as a preventive. In the Ashanti War, 1873, a daily ration of quinine was issued to all ranks, and apparently the experiment received a fair trial, but it was officially pronounced a signal failure. A similar result was experienced in the Malay War of 1875-76, when it was stated that the men who had taken quinine suffered more

severely from malaria than those who had taken none; and, scattered through the annals of tropical medicine, we find numerous other records of unsuccessful attempts to reduce the case incidence of malaria by various cinchona alkaloids in circumstances which would now appear to offer exceptionally promising opportunities for the prophylactic action of the drug. Personally, I can recall several such experiences. One, which was carried out with what was believed to be a full measure of precaution against all sources of error, is specially noteworthy. It was made at a small village on a tidal river at Lumut in Malaya—at that time an intensely malarial station—where each man of a detachment of Sikhs, none of whom had recently suffered from fever, was reported to have taken every morning from the date of his arrival seven grains of sulphate of quinine, but before their period of duty—three months—was over, all had had severe malaria, and eight per cent. of the force had died.

It is impossible at this date to inquire into the reasons of these and many other alleged failures. No doubt there were serious misstatements of fact; and it must suffice to say that these conclusions have been entirely discredited by the results of subsequent investigation. In most cases, recent experiments when properly conducted have been completely successful.

In the President's recently published work on the Prevention of Malaria full details are to be found of the methods and results of the general employment of quinine by the Indian, the Italian, the Greek and several other governments. These remarkable experiments in sanitation are therefore familiar to you, and it is almost unnecessary to do more than instance them here; but I may point out that in 1895 when no quinine was distributed, the total number of deaths from malaria in Italy was 16,464; in 1902, when 2,200 kilos were consumed, it was 9,908; and in 1909, when 23,635 kilos were distributed, it had fallen to 3,463. In the Italian Army, of a total average strength of 205,000, 3,500 men were formerly incapacitated for service every year by malaria, but since the introduction of quinine prophylaxis, that figure has been greatly reduced, and in 1908 there were only 804 cases. Summing up the situation in Italy, Professor CELLI states that in the districts and months of malaria, the prophylactic use of quinine is as necessary as daily bread, and he records the opinion—now fully endorsed by Italian physicians—that the general administration of the drug has had a powerful influence in

modifying the severity and incidence of the pernicious form, which was formerly the prevalent clinical type of the disease.

Not only has the tendency to recurrence been markedly diminished, but the graver manifestations of infection have disappeared, and previous prophylactic treatment renders all forms of malarial fever more amenable to therapeutic doses of the drug.

Still more recent reports show that it is not only in countries where the general standard of education and intelligence is fairly high that these results can be attained. In Algeria, where facilities for the quininisation of the population of malarial districts were introduced so recently as January 1st, 1910, the disease has already greatly decreased in frequency and severity, and a system of educative and persuasive measures, combined with an abundant supply of cheap quinine has had the very best effect on the public health. As a contrast to the Lumut experiment already instanced, and as showing the great value of quinine prophylaxis when detachments of troops, police, etc., are stationed at posts where mosquito reduction is impracticable, the recent case of Ha-tien, a small French military station on the Gulf of Siam may be cited. The district has always been notorious for extreme insalubrity, and of 29 Annamite soldiers there in 1902, 28 were suffering from malaria. After quininisation was begun in January, 1903, there were in that month only 59 days of exemption from duty in a force of 40 men, in February 14, and in March only 2. In August, when the quinine was stopped, there was a severe recurrence of fever, but the outbreak was promptly checked by the resumption of prophylactic doses. A State service of preventive quininisation has now been organised throughout French Indo-China to the great benefit of the general community, and especially to the effective strength of the civil and military forces.

With regard to the rationale of quinine prophylaxis, the question arises :—What really takes place when a man who is living in a malarial district is enabled to ward off fever by dosing himself systematically with quinine? Are free sporozoites destroyed on their introduction into the blood stream, or does the drug act only on merozoites? Are both incapacitated from attacking the corpuscles, or is the intra-corpuscular growth of the trophozoite arrested? So far as the sporulating forms are concerned, it is now definitely known that quinine acts in the circulation much in the same way as it does on the microscope slide, and that the

rapid disappearance of free merozoites after a dose of the drug is due to the circumstance that, in their very earliest stages, the parasites are much more susceptible to its action. The activity of quinine has in fact been shown to be in inverse ratio to the development of a schizont; but except that it stimulates phagocytosis in a marked degree, practically nothing is known of its action—or, indeed, if there is any action—on sexual forms.

The elimination of quinine from the system has naturally an important bearing on prophylaxis. It has been shown that the length of time during which the drug remains in the circulation is roughly proportional to the insolubility of the salt employed; that is to say, if a full dose of a readily soluble salt is given, excretion begins almost at once, and ceases in a comparatively short time after about 70 per cent. of the salt has been cast out by the kidneys. On the other hand, if an insoluble salt is used it does not appear in the urine for nearly an hour, but it persists for several days, although not more than 40 per cent. or 50 per cent. of the quantity taken can be recovered from that secretion. When the gastric functions are normal, a soluble salt of quinine is quickly changed into acid hydrochloride, but with an insoluble salt the change is slower, and sometimes incomplete. In the first instance excretion of the drug takes place almost entirely by the renal epithelium, but a considerable proportion of an insoluble salt passes unchanged through the alimentary canal and can be recovered from the fæces. This invariably occurs when there is achlorhydria, and often when the drug is taken on a full and healthy stomach. I append the results of some recent experiments which I have made to test previous figures and to compare the persistence of two soluble and well-known salts of quinine with three of the more insoluble and less familiar of its compounds:—

TABLE SHOWING THE PERSISTENCE OF DIFFERENT SALTS OF QUININE
IN THE CIRCULATION.

Salt of Quinine.		Solubility.	Doses.	Appeared in Urine.	Absent from Urine.
1	Acid hydrochloride	...	1-1	10 grains	after 10 mins.
2	Bi-Sulphate	...	1-10	10 grains	" 25 "
3	Sulphate	...	1-750	10 grains	" 35 "
4	Tannate	...	insoluble	15 grains	" 45 "
5	Nucleinate	...	insoluble	8 grains	" 1 hour
					after 24 hrs.
					" 48 "
					after 5th day
					" 5th "
					" 5th "

The nucleinate (5 per cent. suspension in sterilized olive oil) was given as an intramuscular injection ; the other salts by the mouth. The test employed was the thalleioquin test with the substitution of solution of bromine for chlorine.

Experience has further shown that, in contrast to its use as a remedy, the best results in prophylaxis are obtained by keeping up a percentage of quinine in the blood ; and the general rule of practice now is that a salt which is readily soluble is employed when it is desired to obtain a germicidal effect with rapidity and concentrated effect, whilst if more permanent and protracted action is required, the least soluble is selected. As curative remedies therefore, the acid hydrochloride and bisulphate are incomparably superior to the less soluble salts, and for purposes of prophylaxis the sulphate, tannate, or nucleinate are usually most suitable. In making a selection cost is generally a consideration of importance, and it may be noted that while the nucleinate is, up to the present, expensive, the tannate, sulphate, and bisulphate are among the cheapest of the salts. The price of acid hydrochloride is higher—about double the cost of the sulphate or tannate.

These principles of prophylaxis are generally agreed, but in practice there has always been considerable divergence of opinion as to the way in which quinine should be administered ; and a variety of methods, indicated for the most part by the names of the authorities who have recommended them, is familiar to all of us. German physicians, for instance, generally prescribe large doses at considerable intervals. KOCH's usual method, and one which he employed with great success at Stephansort and several other stations, was to give 15 grains on two consecutive days at intervals of eight to ten days ; but at Brioni he somewhat modified this arrangement by giving 15 grains daily for three days, and repeating that dose on every tenth or eleventh day after. PLEHN advises one gramme every seven days. On the other hand, American, French, Italian and British authorities mostly concur in the view that the best results in prophylaxis are obtained by small doses given regularly every day. CARTER of the Panama Commission, who states that in the Canal Zone the evidence in favour of quinine as a prophylactic is overwhelming, gives from three to six grains daily, and finds that the only drawback is that the malaria rate has been reduced to so low a figure that the men dispute the necessity for taking quinine, and

are willing to resume prophylactic doses only when several cases of fever have occurred in the camp. In most of the French Colonies, and especially in those in which civilisation is less advanced than in older centres, definite instructions are laid down for the quinisation of the people by a State Antimalarial Service, and a considerable amount of pressure is exercised to enforce their regulations. In certain districts of Algeria, for instance, parents and schoolmasters are required to see that children over three and under ten years of age take 20 centigrammes (about 3 grains) of quinine every morning from the first of May to the first of November; and when local conditions demand it, all inhabitants above ten years are ordered to take 20 to 40 centigrammes daily. In the instructions of the Antimalarial Service Board, emphasis is laid on the fact that the important thing is not to take a great deal of quinine, but to take it regularly every day. Professor CELLI claims that the plan advocated by him of giving a moderate daily prophylactic dose of quinine (six grains for persons over ten years, or three grains for children under ten years of age) to all the inhabitants of a malarial zone during an epidemic, and therapeutic doses (from 18 to 20 grains for adults and half that amount for children) for seven or eight days in every case of acute fever, is the most simple, inexpensive, and efficacious method. Where circumstances do not permit of a daily dose being taken, two weekly doses of 15 grains each (on Saturday and Sunday evenings) are substituted.

In Italy, a remedy known as Battara's pillules, in which arsenic is combined with quinine, is in very general use. The formula is as follows:—

R. Quin. Bihydrochlor	...	...	...	1½ grs.
Ferri Citratis	...	...	...	½ gr.
Acid Arsenios	...	...	...	1/64 gr.
Ext. Gent.	...	...	...	2 gr. <i>m ft.</i> pil.

When taken as a prophylactic, two pills are given every morning. British physicians generally recommend the daily administration of three to five grains, and CASTELLANI advises for adults five grains daily for six days, with a double dose—ten grains—on the seventh, and for children, one grain daily for every three years of age.

By far the most serious objection which has been urged to the prophylactic use of quinine, is the possibility that the routine use of the drug in health may increase the frequency of blackwater fever as a

complication, when malarial infection does take place. But a careful examination of the literature and statistics proves that even in countries where blackwater fever is endemic, there is no ground for this serious apprehension. On the contrary, STRACHAN and others have shown that in West Africa, where almost all the Europeans take quinine as a prophylactic, the case incidence of malaria amongst Government officials is now only a fifth of what it was in 1900 when very few took quinine, whilst that of blackwater fever remains approximately the same. In the medical reports of the German Protected States in West Africa for 1908-09, it is stated that at Dar-es-salem all malaria carriers, 4,578 in number, were given a course of quinine. In most of the cases the course lasted three months, and was carried out as follows:—On two successive days of each week adults were given 15 grains of quinine in tabloids or solution, the medicine being invariably taken in the presence of a European; children received a proportionately smaller dose in a sweet solution. In only four cases was an attack of blackwater fever induced by this treatment; all recovered, and the patients were afterwards put through an acclimatization course of gradually increasing doses of quinine until complete tolerance of the drug became re-established.

In conclusion, the present position may be briefly summarised as follows:—

1. Quinine prophylaxis is now fully accepted as an auxiliary method of the greatest importance in the prevention of malaria; it is essential in dealing with infected native populations, and is specially valuable when (as in the case of detachments of soldiers, railway employees, etc.) general measures are out of the question, individual control and supervision being on the other hand practicable.

2. When general quininisation of a native community is advisable, it should be carried out systematically on an approved plan by a special staff of distributors under a medical director.

3. The most suitable salts for purposes of prophylaxis are the sulphate, tannate, and nucleinate, and the best method of administration is a daily dose of three to five grains for adults, and for children (for whom the tannate is best adapted) one grain daily for every three years of age.

Dr. C. F. HARFORD: The matter of quinine prophylaxis is, in my opinion, of the greatest practical importance, and there is real danger of this being neglected.

In particular, it seems to me that it has not received the support which it deserves from the medical profession. I have the serious responsibility of advising a large number of missionaries, going to all parts of the world, with regard to the preservation of their health, and my experience has been that many of these who have gone out with instructions as to the taking of quinine, so soon as they arrive are told by medical men on the spot that there is no need to take quinine, with the result that the instructions given are ignored. Holding the views I do, I naturally regard this state of things with alarm, as I feel that those who neglect quinine are not only endangering their own health, but are inducing a feeling of indifference in their companions to the drug that will seriously affect the well-being of our missionaries.

In West Africa the taking of quinine is well carried out, and that this is so I attribute chiefly to the splendid efforts of Sir WILLIAM MCGREGOR. His work in Lagos has done more than anything else to popularise the drug in West Africa. Almost every one of our missionaries takes quinine as a prophylactic, 5 grains a day, and I strongly recommend it to be taken in this manner.

On the East Coast of Africa and in Uganda many of the Europeans have a profound distrust of quinine. The idea is disseminated that quinine is going to produce blackwater fever, and I have the greatest difficulty in persuading missionaries in that part of the world to take quinine as a prophylactic, especially as, in most cases, it is impossible to carry out a large reduction of anophelines. Dr. CARNEGIE BROWN has mentioned the fear of blackwater fever as an important objection to taking quinine, but it is a remarkable thing that the Germans, who were perhaps responsible for the theory that the taking of quinine gave rise to blackwater fever, now teach that quinine is the drug which must be employed to prevent its occurrence. KOCH said that if a man had blackwater fever, and after the attack was over took small doses of quinine and then full prophylactic doses, he would never contract either malaria or blackwater fever again. This may rather overstate the case, but the German statistics go to show that quinine is just as likely to prevent blackwater fever as malaria.

As regards the salt of quinine to be used, I am not at all convinced which is the best. Our missionaries use bisulphate of quinine; it is the cheapest and gives very satisfactory results. Dr. OLPP, who is a Fellow of this Society, sent me some notes on this question, but as they are practically a résumé of what has appeared in the President's work, he felt they were not sufficiently new to bring before the Society. He, however, stated that Germans were in favour of giving hydrochloride of quinine. I should be very glad if someone present could state authoritatively what is the best salt of quinine to give. For my own part I do not think it matters much what salt is given. What, however, I think is of importance is that the taking of quinine should be kept up sufficiently long. Patients forget that after having been in an infected district they may still be infected after they leave, and that it is only by means of quinine that they can keep down the influence of the infection after having left a district, especially when they come home. Bad cases arise in England merely because patients give up quinine directly they get on board ship bound for home.

Dr. A. T. OZZARD: No one who has practised in the Tropics can deny the value of quinine prophylaxis, but I think its advocates carry it too far as against measures for the eradication of mosquitoes. When they talk of quinine prophylaxis they push other matters in the background. I have been giving quinine regularly since 1900 in the Reformatory School in Demarara, and I am quite sure it has kept the prevalence of malarial fever there in check, but it has by no means eradicated it and never will. Taking the diseases of that school, malarial fever always heads the list. I think the advocates of quinine prophylaxis are in error in urging their views to the exclusion of the method of eradication by destruction of the mosquitoes. I am quite sure if a comparison was made of results from expenditure on quinine prophylaxis and expenditure on eradication methods, the latter method would give far larger benefits.

Professor W. J. SIMPSON: I gather that this paper is not brought forward with the idea of comparing quinine as a prophylactic with mosquito destruction or other measures, but that the subject is dealt with more from the point of view of the value of quinine taken as

a prophylactic in a malarious country. A few months ago I was in a library looking for some books, and happened to take up a volume which contained much of the evidence on which the recommendations of the United States Sanitary Commission of 1861 were based. In this volume there was a paper with a title similar to that read to us this evening, and which showed that as far back as fifty years it was an established fact—according to the writers and also according to the recommendations made by that Commission—that quinine was useful as a prophylactic. Some striking evidence was given in that paper taken from various sources. One case in particular, which is worthy of mention, was that of a railway contractor who was laid up with malarial fever and was attended by a doctor. This man expressed his anxiety about the carrying out of a contract that he had entered into, because he had to bring 150 workmen into a very malarious district from a non-malarious one to carry out the work. His medical man (after curing the patient) advised him to take quinine himself and give it to all his workmen regularly. The contractor did so, with the result that these 150 workmen were able to carry out this contract without one case of malaria occurring.

Another interesting point was the mention of Dr. ALEXANDER BRYSON's recommendations, in 1847, to the Admiralty, that quinine should be given to the sailors who were on the West African coast instead of bark. It was to be given in the form of quinine wine, one ounce of the wine containing four grains of quinine. He also suggested that not only should quinine be given during the time the sailors were up rivers or on shore, but for fourteen days after they had returned on board ship. This, he stated, was in order that the quinine should continue to act until the end of the period of incubation. I need not trouble you with details, but these suggestions were accepted by the Admiralty, and quinine wine was added to the medical stores of the cruisers employed on the African station with most satisfactory results.

I quite agree with previous speakers that it is better to give quinine regularly in small doses such as five grains. I think one has seen more benefit derived from this than from other methods. It is not likely to be forgotten if put on the table regularly. For myself, I always found if taken in the evening it caused me a sleepless night, whereas when taken in the morning it suited me very well.

I also agree with the conclusions as summarised by Dr. CARNEGIE BROWN, and I think most of us will concur in his view that it is a proper precaution to be taken by those in very malarious countries. I do not think it is necessary to take quinine continuously in countries that are only malarious at certain times. I used to take quinine in Calcutta during the rains, but at no other time, and I always managed to escape fever. Calcutta is not very malarious, but sufficiently so during the rains to cause a certain number of cases.

Dr. BASIL PRICE: There are one or two questions I should like to put.

In the first place, one often finds that individuals who when abroad are unable to tolerate quinine in the usual doses, can take smaller ones. I should like to know if, in these cases, small doses such as 1 or $1\frac{1}{2}$ grains, are of any real use from the point of view of prophylaxis or treatment.

Some interesting experiments have been quoted as to solubility and absorption of various salts of quinine in the stomach; have similar experiments been carried out with regard to quinine being administered per rectum? If anything has been done in this way with quinine it would be interesting to know the results.

There is also the question of quinine deafness to be considered. What pathological change follows the taking of quinine and is it a fact that the deafness is persistent after the use of quinine has been discontinued?

Also, is it a fair test, when patients can tolerate the use of quinine in this country, to judge of equal tolerance of the drug when taken abroad?

Then again there is the question as to how long an individual coming back to a cold climate should take quinine after leaving the Tropics. I suppose there is no blood test to determine this, but that it must depend on the result of accumulating experience.

I should be glad to have information on these points.

Major W. S. HARRISON: The intolerance of quinine, referred to by Dr. PRICE, has been observed by me in members of my own family for three generations, all of whom have been quite unable to take quinine because of consequent urticaria. The quantity given, whether ten, five

or even one grain, did not seem to matter, the result was the same—an attack of urticaria.

With regard to the general question of quinine prophylaxis, I think those who work for public bodies should keep this as an emergency method, for the reason that there is a strong temptation for a public body to prefer the method showing the lowest initial cost at the expense of the more effective process. I am certainly of opinion that anti-mosquito measures should be tried whenever possible, and quinine prophylaxis only resorted to as a secondary measure.

Dr. F. M. SANDWITH: I am glad this discussion has taken place. I agree with the last speaker as to quinine prophylaxis, but I presume the writer of this paper had before him the question only of *personal* prophylaxis in a country where malaria is endemic, and I think we should have proper regard to this fact in offering an opinion or criticism, because our remarks will, when printed, go to many of our colleagues and friends abroad who are specially interested in malaria.

Certainly mosquito prevention ought to be our first line of defence, and we all know, Mr. President, that you are in favour of this. We should be perfectly certain of our ground in this matter. After mosquito prevention we come to quinine prophylaxis as a personal measure, and it is only that which we are discussing to-night. One of the first questions which occurs to me is as to the choice of the salt. For children I think we all accept—as the writer does—tannate of quinine as an excellent remedy. As regards adults, there are a large number of salts, and you have first of all to decide whether you agree with Dr. BROWN as to giving a soluble or insoluble salt. Dr. HARFORD is of opinion that this question is not of supreme importance, but for myself, I cannot pretend not to have my favourite salts. I think there is nothing to be gained by giving an insoluble salt provided you give quinine often. If you only give quinine once every 4 or 5 days then perhaps the insoluble quinine is better, but if quinine is given every day then I cannot see why an insoluble salt is preferable. I have asked manufacturers why the sulphate is so much used, and the only reason they give is that the average practitioner has not discovered the existence of other salts. Then when I ask whether there is any advantage in using sulphate in preference to bi-sulphate, they reply that the action is the same but the

sulphate is inconvenient because it needs so many parts of water to dissolve it. We all know the disadvantages of giving sulphate of quinine either in the form of the coated pills which were formerly used or in tabloids, because it has been found that the pills and tabloids returned to world undissolved. It seems much better to me to use a drug which acts directly upon the system instead of using one which is absorbed slowly, or requires acid to dissolve it.

As regards price, if large quantities are bought as for an institution, there is a distinct advantage in using bisulphate, for in this form quinine only costs 10d. an ounce, whereas the bi-hydrochloride is more expensive and costs 16d. an ounce.

With reference to blackwater fever I think most of us will admit that although you can produce blackwater fever (I am sorry to say I have once done it by giving quinine in England to an Anglo-African who had never had it before) this fever can be entirely prevented by giving regular and constant doses of quinine. Given in this way one hardly ever hears of blackwater fever, but if the quinine is taken irregularly then of course a large dose of quinine may be followed by blackwater fever.

As regards dosage it seems there are only three methods worthy of discussion, *i.e.* :—

- (1) Two doses of 10 grains on successive days of each week.
- (2) Five grains per day; or
- (3) Five grains per day with an extra five grains on Sunday.

I used to advise the first method, but I have been compelled to give it up because I found that although a certain number of patients who had returned from Africa, and who had been taking quinine by this method, remained free from fever, others had it; whereas patients who had taken five grains of bi-hydrochloride of quinine every day never had any recurrence.

I may quote here a case of blackwater fever, which is interesting in connection with the first paper of this evening, because the patient died of this fever not far from the Zambesi river. He was a healthy football-playing schoolmaster, aged only 21, and whilst in Africa had had four mild attacks of malaria. During these attacks his temperature rose to 103°, but the day following this rise it is said to have fallen to normal. He became infected during a few days spent at Delagoa Bay, and did not begin prophylactic quinine until his arrival at the Zambesi river, when

he took 10 grains daily while on the river and 10 grains twice a week afterwards. Yet he died in 10 months after his arrival in Africa of blackwater fever.

I think quinine should be continued for at least a month after patients leave an infected country, or for three months after their last attack of malaria.

As regards the idiosyncrasy to quinine poisoning, or to quinine deafness, it seems to me that candidates ought to be first tested in this country; if there is any doubt as to the individual being able to take five grains of quinine a day without suffering from deafness or other troubles, that person should be advised to live in a non-malarial country.

Dr. L. E. WIGRAM : In reply to the question raised as to intolerance of quinine, I may mention the case of a patient who had to go to bed at once if he took a 5-grain dose of quinine with racking headache and urticaria. He was, however, able to take a 2-grain dose of euquinine in solution, three times a day, without the appearance of these symptoms, and the fever yielded in a few days to this treatment.

The President (Professor RONALD ROSS) : We have been carrying on researches in connection with this subject for some time. In every case the parasites in a thick film have been counted, and we have been able to tell the effect of quinine in a much more thorough way than has ever been done before. The results as regards dosage have been in favour of larger doses, which would seem to point to the fact that we have often been giving prophylactic quinine in too small doses. Judging from the results of our experiments we find roughly that it requires daily doses of from 15 to 30 grains for five days to kill all the parasites in a thick cubic millimetre of blood. These results, however, apply to the asexual parasites. In the case of the sexual parasites, doses of these amounts had no effect for ten days. We know that crescents take ten days to develop. After this period they tend to become reduced by continuous dosing; but it takes quite fifteen days before quinine knocks them out to a large extent. Many observers have noticed this, and I remember Sir PATRICK MANSON telling it to me many years ago; but we have now obtained exact estimates. All this is, I think, important prophylactically.

As to method of action, we have been trying to find the rationale as to what quinine does in malaria. We tried several enormous doses on cases which were not malaria, and we could find no hæmolytic action *in vivo*. It may cause a leucocytosis, but a very slight one. I thought for a time quinine may destroy the parasites by hæmolytic action; that the corpuscles containing the parasites would be weakened, and thus more readily dissolved. I do not now think there is any evidence of this; and we are still at a loss as to why quinine should act as a specific. It is curious, too, that it affects such a very small group of organisms *in vivo*.

As regards what salts of quinine should be used, I think that the soluble salts are best for treatment and the insoluble for prevention, as Dr. CARNEGIE BROWN says. But I think I agree with Dr. HARFORD that the difference is inappreciable. As to the dosage, it is a question whether small doses of quinine do not suffice merely to reduce the number of parasites. Suppose that the dose given is too small to eradicate the parasites entirely, what dose will produce a reduction to a given percentage? A small dose might make some difference in the fever rate, but not much in the infection rate; that is to say, there would be less actual fever, but there would still be the same number of persons infected.

As to length of treatment, I have read an excellent paper on this question, in which it is shown that after four months' dosing by 10 to 15 grains of quinine, relapses occurred in about 2 per cent. to 6 per cent. of the total number of cases* I have always taught that four months' dosing of quinine was necessary; but I now think we ought to give either much larger doses for this period or small doses for a longer one. It would be a good plan, I think, to institute what I would call a "Quinine Lent." In other words, to fix upon the month just before the anopheline season, during which all the cases should undertake the tribulation of quinine, with the addition of perhaps another month at the end of the malaria season for the same purpose. The difficulty here, however, is to get people to do this.

With regard to mosquito reduction, I agree very largely with the two previous speakers on that method. Quinine prophylaxis is a refuge for large public bodies. They will not, or cannot, spend money on

* Capt. A. B. SMALLMAN, *Journ. Army Med. Corps*, May, 1911.

mosquito reduction, and they advocate the taking of quinine because it is the cheaper method for them. But as to the comparative expense of these two methods, I have always endeavoured to emphasise the point that a doctor is required for the giving of quinine and coolies for mosquito reduction. A doctor costs as much as 50 coolies. In India the average cost of a doctor is, say, 500 rupees a month. This amount would keep at least 50 or 60 coolies going. Just consider the amount of mosquito reduction which would be accomplished in a village by this number of coolies!

In the vast majority of cases, however, it is better, if possible, to do both, viz., give quinine and attend to mosquito reduction. In my opinion, quinine is especially useful in slightly malarious areas: in Italy, for instance, where malaria may not be so generally intense as in many places in the Tropics.

Sir PATRICK MANSON: I should like to ask Dr. CARNEGIE BROWN to define exactly what he means by the expression "Quinine prophylaxis." Does he mean prevention of infection, or, merely, prevention of the clinical manifestations of infection? Personally I do not think that even the most scrupulous and regular ingestion of quinine prevents infection, for I have over and over again seen persons who had dosed themselves systematically over long periods and yet must have become infected as proved by their exhibiting, perhaps for the first time, clinical evidences of malarial infection weeks or months after they had quitted the endemic area. The point is of some importance, for if quinine prevents infection there can be no object in continuing prophylactic dosing after leaving the endemic area; but if it merely prevents the clinical manifestations of infection then it should be continued many months after the patient has regained a non-malarious country. The public generally, and certain members of the profession are not quite sure on this point.

Dr. CARNEGIE BROWN in reply said: Most of the points raised in the discussion have been already answered by previous speakers, and as regards the question asked by Sir PATRICK MANSON, it concerns the rationale of the action of quinine rather than the definition of quinine prophylaxis. That, as I have said, is a very difficult problem. I endeavoured to define quinine prophylaxis in my paper as placing the

system in such a condition by taking quinine that a man, who has been inoculated by infected anophelines and who otherwise would have developed symptoms of malaria, remains free from fever and fails to exhibit the usual consequences of infection. It has not yet been shown how that result is secured, or in what manner, or at what stage of its growth the suppression of the parasite is effected.

With regard to the President's remark that we are probably giving too small doses for effective prophylaxis, it may be noted that the general tendency is to decrease quantities; and foreign physicians, who have very large experience of quinine used as a prophylactic, order even smaller doses than is customary in the English School. Our usual prescription is at least 5 grains daily, and Americans mostly follow us in that rule, but in Germany, Italy, France and Greece, the quantity recommended for daily consumption is generally 20 centigrammes, or about 3 grains. Personally, my experience has been that fairly large doses—5 to 6 grains—are necessary to give good results in prophylaxis, and naturally, a very much larger quantity is required when the remedy is employed for curative purposes.

As to the question of quinine deafness, I agree with Dr. SANDWICH. I would go further and say, that in the case of patients who come for examination previous to being engaged for service in a malarious district, where it is probable that they will have to take quinine, an effort ought to be made to find out whether they can tolerate full doses of the drug. Although tolerance can generally be established afterwards, a grave risk is incurred by those who are intolerant of quinine taking up their residence in a malarious region; and the test of capacity to take 10 or 15 grains of the remedy should be made in this country, and not when they are suffering from a severe infection, and possibly where blackwater fever is endemic.

Finally, with reference to the contrast between quinine prophylaxis and mosquito campaigns, which has been drawn by one or two speakers, I may say I had no intention of making any comparison between these methods as preventives of malaria. It cannot be too clearly understood that quinine prophylaxis must always be an auxiliary measure; and I sincerely trust that my remarks have not led any one to believe that it is yet possible to dispense with a single precaution in the campaign against the carrier of the disease.