apparatus, the great distance-receptor of the head, that the functions of the labyrinth derive so much of their importance in human physiology.

"The function of the labyrinth is to keep the world right side up for the organism by keeping the organism right side up for the world."[36] This statement is peculiarly apposite in the case of those who explore the air, since it is by reason of the pre-eminent influence of visual sensations and the necessity for their accurate adjustment that the labyrinth gains its true significance for the pilot. We can, therefore, rest content in the knowledge that our conceptions of labyrinthine activity during flight harmonise with those broad conceptions of the activities of the nervous system in general, and of the labyrinth in particular, which science owes to the brilliant researches of Sherrington and his even more brilliant interpretations.

CONCLUSION.

In these lectures an attempt has been made to portray the mental and bodily mechanisms by which the healthy organism strives with varying success to counteract the abnormalities of its surroundings. It is difficult to avoid the conviction that were we to adopt a somewhat similar attitude in studying the functional reactions of the organism to abnormal processes arising not from without but from within itself—viz., the processes of disease—we should realise more than we do now that some at least of these reactions are not merely consequential and nocuous but rather compensatory and beneficial. It would, further, appear that some such attitude is likely to foster a closer working alliance between the science of medicine and the more exact sciences on which it is founded, an essential preliminary to the advancement of medical thought and consequently of medical practice.

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AT the Crystal Palace on June 19th, 22nd, 24th, and 26th the Handel Festival will be held, we understand, on a larger scale than ever.

RESEARCHES ON THE TREATMENT OF BENIGN TERTIAN FEVER.

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THE results obtained with the help of my co-workers, Dr. Dagmar Curjel, W.M.S., and Assistant Surgeon J. O. Dewey, I.M.D., whilst I was in charge of the Malarial Research Laboratory, Dagshai, appear to me likely to lead to important advances in the treatment of these fevers. Hitherto the treatment of malaria was summed up in one word, "quinine," and the only points at dispute were the methods of administration and the length of time this alkaloid should be taken. The other alkaloids of cinchona bark have been used by numerous observers, but as far as I am aware have never been accurately tested. MacGilchrist (1915), who made the most systematic trial hitherto recorded of these alkaloids, was unfortunate in having to test them under conditions where reinfections could not be excluded and where the cases could not be observed sufficiently long to exclude all the relapses. The universal belief that quinine is equally a specific for all types of malarial fever will have to be abandoned before any material advance can be made in the treatment of these fevers. Malarial fever should be regarded not as one disease, but a group of three different fevers, due, as is already known, to three distinct parasites, and two at least of these require different alkaloids of cinchona bark for their treatment. After making such a dogmatic statement, I will first explain how quinine came to be regarded as a specific for all three types of malarial fever.

Quinine invariably exerts an immediate effect on all three types of malarial infection, causing a rapid amelioration in symptoms and disappearance of the asexual parasites from the peripheral blood. The annihilation of every asexual parasite in the body, or the prevention of relapses, is, however, the only test by which one can truly estimate the specific action of these alkaloids. From the present statistical evidence it is almost impossible to estimate the degree to which this complete cure or sterilisation has been attained, as the figures are markedly influenced by one or more of the following factors:—

(1) In the tropics quinine has to be administered under unfavourable circumstances—viz., under epidemic conditions—and reinfections may occur as soon as the quinine is withheld. This effect may give rise to too unfavourable an impression as regards the cure-rate.

(2) Cases are often not observed much longer than the duration of treatment. Many of the relapses are not seen by the same medical officer, and in this way too favourable a clinical impression is created as regards the curative value.

(3) The microscope is not sufficiently employed. Fevers are often diagnosed as "malaria" from symptoms only, and malignant tertian infections from the presence of pernicious symptoms.

In spite of these factors, which may cause an unduly favourable or unfavourable estimate of the sterilisation-rate, there is a general clinical impression that these three fevers relapse after quinine treatment, in the following order of frequency: quartans most frequently, then benign tertians, and malignant tertians least frequently of all. This corresponds to our own experience, that the cure-rate produced by quinine in the three types of fever is as follows: 90 per cent. or over in malignant tertians, 20 to 30 per cent. in benign tertians, and under 20 per cent. in quartan infections.

The Test of a Cure.

Many of the previous workers on the action of the cinchona alkaloids were compelled to work under unfavourable conditions. Stephens and his co-workers had to a large extent laid down the conditions that were necessary for the test of a cure. We were more fortunate in treating British troops under our immediate command, where every detail could be followed in the treatment. Every one of our recorded cases remained for two months or longer under observation after completion of treatment. The adverse factors already mentioned did not affect our figures, as they could be prevented by—

(1) The exclusion of reinfections amongst our cases during treatment and observation. Dagshai is situated on

an isolated hill-top at 6000 feet above sea-level; there are very few sites suitable for breeding-places for the anophelines, and the temperature conditions are, for the greater part of the year, unfavourable for the fertilisation of the female gamete.

(2) Every case recorded as a cure was observed for at least two months, sometimes longer. This observation time-limit, first suggested by Stephens, was tested by plotting every parasitic relapse that occurred amongst our benign tertian cases. These relapses numbered 978, and are shown in the following table.

Table I. shows the frequency distribution of 978 parasitic relapses, all due to the benign tertian parasite, which occurred during and after treatment, and are shown in intervals of weeks.

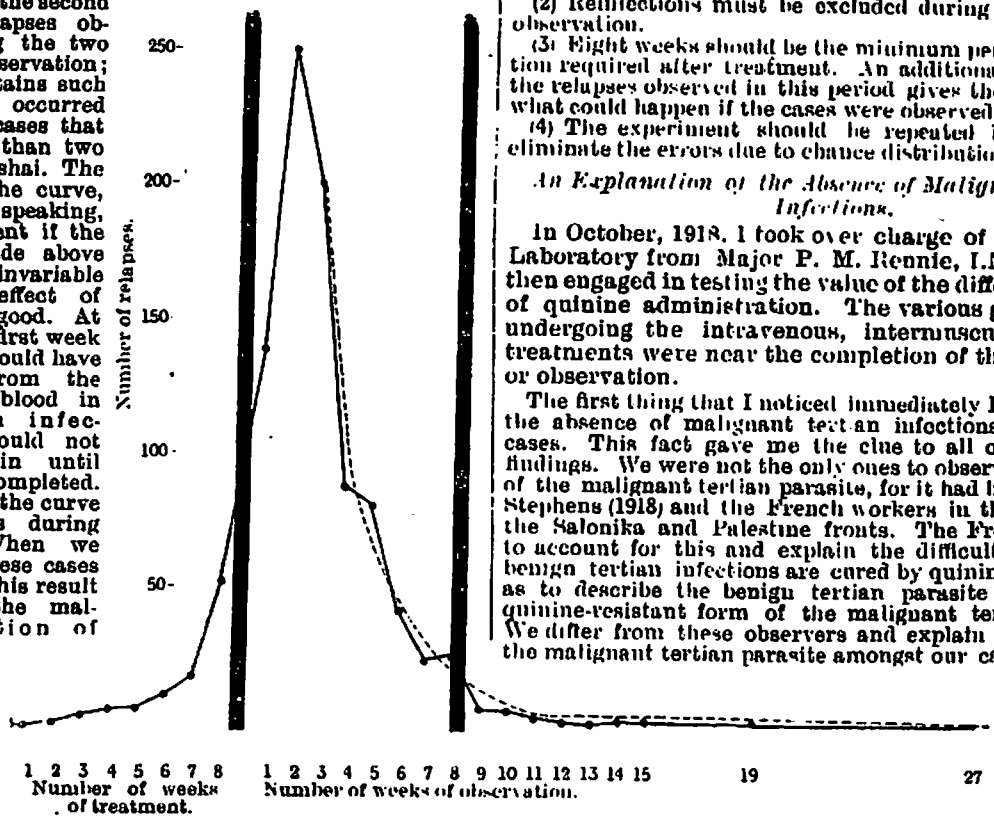
TABLE I.

(A) Interval of weeks. (B) Number of relapses.

	During treatment								After treatment.														Total.
(A)	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	19	27	—
(B)	—	1	4	6	7	12	19	53	139	248	199	89	82	43	25	26	7	6	4	2	1	2	1	1	1	978

These results are better depicted in the form of a graph, which is here shown. The two vertical bars divide the curve into three parts. The first part contains the relapses observed during the eight weeks of treatment; the second part the relapses observed during the two months of observation; the third contains such *relapses* as occurred *amongst* the cases that stayed longer than two months in Dagshai. The first part of the curve, theoretically speaking, should be absent if the statement made above about the invariable *immediate* effect of quinine holds good. At the end of the first week all parasites should have disappeared from the peripheral blood in benign tertian infections, and should not be seen again until treatment is completed. Instead of this the curve gradually rises during treatment. When we investigated these cases we found that this result was due to the mal-administration of quinine, by patients avoiding treatment, intermittent types of treatment, and too large doses. As soon as these factors were recognised and corrected no further parasitic relapse occurred during treatment.

Graph showing Frequency Distribution of 978 Parasitic Relapses.



The second part of the curve shows the time frequency of the relapses that occur during the two months' observation after treatment. As the first part of the curve is due to an error it is not included in the calculation of the mean and standard deviation. The mean of these figures is at 3·404 weeks, and the standard deviation is ± 2·42 weeks, indicating that three-quarters of the relapses occur between the first and sixth week after treatment. The eight weeks' period of observation after treatment laid down by Stephens is a sound practical period to test a cure, as it includes over 90 per cent. of the relapses that may occur after treatment. The third part of the curve from the ninth week onwards could not be accurately determined by us, as we could not keep the men indefinitely away from their units during war. I consulted Professor Karl Pearson, F.R.S., to see if he could help me to obtain some idea at which po nt this curve might possibly end. I must thank him for the trouble he has taken to work out the figures. He tested them by two different methods and found that the end-point occurs somewhere about the thirty-sixth week—that is, in benign tertian infections, if the blood is examined every week for nine months and no parasites are found, the case can be regarded as an absolute cure. A rough estimate of this portion of the curve can be arrived at by drawing a free-hand curve from the point at three weeks to the thirty-sixth week, shown as a dotted line in the graph. This portion represents another 6 per cent. of relapses on those already observed during the eight weeks of observation. This additional 6 per cent. gives the necessary correction to obtain the total number of relapses that would occur if the cases were observed for the full nine months after treatment.

(3) The parasite was seen microscopically in every case before the patient was placed on treatment. Individuals harbouring the same species of malarial parasites were tested together under the same conditions. In much of the older work the three species of parasites were indiscriminately mixed up in the same treatment groups.

Stephens (1918) suggested that a seasonal influence was present in his cases, which appeared materially to affect the cure-rate. In an article now in press we have dealt with this point, and consider that the error of chance distribution could explain the variations in cure-percentage better than any seasonal influence. It is immaterial which explanation is correct, but we know that such fluctuations do occur, and a repetition of the test would settle the question whether a cure-percentage was accurate or not.

The conditions required to test a particular cure for malarial fevers may be summed up briefly—

(1) The population under investigation should be sufficiently large and homogeneous. At least 100 men should be treated, and the parasites must be of the same species and found microscopically in every case.

(2) Reinfections must be excluded during treatment and observation.

(3) Eight weeks should be the minimum period of observation required after treatment. An additional 6 per cent. on the relapses observed in this period gives the correction for what could happen if the cases were observed longer.

(4) The experiment should be repeated if necessary to eliminate the errors due to chance distribution.

An Explanation of the Absence of Malignant Tertian Infections.

In October, 1918, I took over charge of the Research Laboratory from Major P. M. Rennie, I.M.S., who was then engaged in testing the value of the different *methods* of quinine administration. The various groups of men undergoing the intravenous, intramuscular, and oral treatments were near the completion of their treatment or observation.

The first thing that I noticed immediately I took over was the absence of malignant tertian infections amongst our cases. This fact gave me the clue to all our subsequent findings. We were not the only ones to observe this absence of the malignant tertian parasite, for it had been noticed by Stephens (1918) and the French workers in their cases from the Salonika and Palestine fronts. The French, in order to account for this and explain the difficulty with which benign tertian infections are cured by quinine, went so far as to describe the benign tertian parasite as an altered quinine-resistant form of the malignant tertian parasite. We differ from these observers and explain the absence of the malignant tertian parasite amongst our cases as due to the specific action of quinine, for all our cases had undergone a course of treatment with this alkaloid before arrival at the depôt. This statement is based on the following data.

(1) Out of 992 parasitic findings only 14 individuals were found to harbour the malignant tertian parasite. There were 978 showing benign tertian infection.

(2) At this depôt our experience of malignant tertian infections was small, but every case treated by quinine was cured. This corresponds with the experience of Thomson (1917) and Barlow (1915). Thomson estimates the cure-rate at 80 per cent. and Barlow at 100 per cent. if treatment were continued for a month.

(3) Our cases were drawn largely from the Punjab, a province where there is a seasonal prevalence of these two parasites, benign tertians at the beginning and malignant tertians at the end of the hot weather. In spite of this seasonal prevalence the malignant tertian parasite was rarely found, as all our cases had been treated with quinine before arrival at the depôt.

(4) One hundred and two men had been diagnosed as malignant tertian infections, crescents being noted in their

medical history sheets. These men had been treated with quinine at their units in the plains. In Dagshai they only received an iron tonic. There were no malignant tertian relapses, 64 relapsed with benign tertian infection, and 38 did not relapse. This preponderance of benign tertian relapses in a malignant tertian series is probably due to double infections, as it is difficult to see how the pathologists could have made an error in diagnosing crescents.

(5) In a similar series of 102 different men diagnosed as benign tertian infections these parasites were noted in their medical history sheets, and the men were treated exactly as the group above. There were 76 benign tertian relapses, no malignant tertians, and 26 did not relapse. The lower cure-rate in benign tertian infections should be noted and the absence of malignant tertian relapses in both series.

The specific action of quinine on the malignant tertian parasite explains how this parasite disappears from the blood of malarial patients who have returned home from the tropics, as such individuals have been well drugged with quinine.

The Low Sterilisation-rate of Quinine in Benign Tertian Infections.

The second important point that became apparent after we analysed our results was the low cure-rate of quinine in benign tertian infections. Out of 663 cases of this infection treated with quinine there were 32·4 per cent. of cures; nearly 70 per cent. of the cases relapsed in spite of treatment. The series of cases given in Table II. were commenced in Major Rennie's time and completed by us. The results obtained were as follows.

Table II. gives a comparison of the results we obtained by the different methods of quinine administration in benign tertian infections.

TABLE II.

Method.	No. of cases.	Cure per cent.	Duration of treatment.	Quinine in grains per course.
(A) Intravenous combined with oral	100	18	4 days to 8 weeks.	48 to 678
(B) Intermuscular combined with oral	94	27·6	8 weeks.	1284
(C) Oral alone—				
(1) Stephens' intermittent 45 gr. per diem for two consecutive days weekly	90	18·8	8 ,,	720
(2) Stephens' intermittent 30 gr. per diem for two consecutive days weekly	113	30·0	8 ,,	480
(3) Ross and Thomson's method continuous for four months	76	52·6	16 ,,	1980
(4) Continuous for ten days 30 gr. per diem	190	42·1	10 days.	300

Comments.

(1) The duration of the treatment is an important factor in the cure. Rennie found that both in the intravenous (1 to 5 injections) and intermuscular (12 injections) groups the injections had to be followed by an oral treatment, lasting in all two months, in order to obtain a better apparent percentage. In the long continuous treatment (Ross and Thomson), extending over a period of four months, the cure-percentage worked out at 52·6, or double that of the two months' courses.

(2) The method of quinine administration did not materially affect the cure-rate. The intravenous method gave the best immediate results and caused the parasites to disappear from the peripheral blood quicker than the other methods. The absolute cure-rate was bad, as the first few cases were only given 2 to 5 injections, which were not followed by quinine orally.

(3) The cure-percentage was low in all the courses of two months, and varied from 18 to 30 per cent. The short continuous course of ten days gave a higher cure-percentage than was expected—i.e., 42·1 per cent. It is possible that the error of chance distribution made this figure unduly high, but it must be noted that another rather serious and unknown error was introduced into the group by the fact that some men bought quinine during the period of observation and administered it to themselves. The latter factor only affected this group in one series, as the armistice had been declared and the men were anxious to return to their units in the hope of getting home quicker.

We are therefore able to confirm the fact that quinine has a low rate of cure in benign tertian infections. This has already been shown by numerous other observers.

The Cause of the Preponderance of Benign Tertians Amongst our Cases.

The malarial population we investigated at Dagshai was a selected one. This selection was brought about by quinine, as all our cases had received a course of this drug before arrival at the depôt.

We have already stated that quinine exerts a highly specific action on the malignant tertian parasite, and therefore practically eliminates this parasite from the cases which have undergone a good course of treatment. The cure-rate of quinine for benign tertians is low, and under such conditions quartan and benign tertian infections will relapse owing to the failure of quinine and appear again and again amongst a treated population. Quartans form a very small proportion of the cases (this infection is relatively rare in the Punjab) and can be neglected. The infection seen amongst a treated population in a non-infected area is practically all due to the benign tertian parasite.

The Effect of Repeated Courses of Quinine on Benign Tertian Infections.

After I had analysed our Dagshai results and seen the low cure-rate of quinine in benign tertian infections, I considered that by giving short courses of treatment a larger number of effective men could be obtained in a shorter space of time than by giving the long courses of four months quinine treatment advocated by Ross and Thomson. The results of this experiment are shown in Table III.

This group consisted of 475 men who had been treated by quinine for malaria and sent up to Dagshai, where they were placed on an iron tonic. Out of these, 277 relapsed, and benign tertian parasites were found in every one of these relapses. Out of these 277, 204 could be observed for the full two months after a further course of treatment, and of these 145 relapsed. Ninety-five could be followed for the full period after the second course of treatment at Dagshai, and 76 relapsed; 45 of these could be followed after the third course and 32 relapsed. Ten of the 32 relapses could be followed after the fourth course, and 8 relapsed. The actual cure-rates for these four courses at Dagshai work out at 28·9 per cent., 20 per cent., 28·28 per cent., and 20 per cent. respectively, or an average of 24·4 per cent. for each course of treatment. The maintenance of the cure-rate about a constant of 25 per cent. from the first to the fourth course of treatment is a very important fact, as it indicates that neither does the parasite become more and more quinine resistant, nor does the host's resistance alter; otherwise the cure-percentage should diminish with each subsequent course. Clinically one cannot say whether a given case will be cured with one or many courses; it seems immaterial whether the patient is undergoing his first or fourth course, for with each course he stands an equal chance of cure.

Whatever explanation may later on be advanced to account for this result, it shows that the cure-rate is dependent on some chance factor.

TABLE III.—*Intervals in Weeks during which Relapses Occurred.*

No. of men in each group.	Treatment.		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	Total No. of relapses.	Total No. of cures.
475	Treated on the plains and observed in Dagshai		115	76	30	20	10	6	6	7	1	1	1	-	1	2	1																							277	198
204	Courses of quinine treatment in Dagshai.	1st				4	4	15	10	6	12	22	12	15	3	7	9	7	6	5	1	5	2																	145	59
95		2nd								1	1	5	1	3	4	4	4	2	4	7	2	5	10	6	3	3	1	1	5	2	1	-	1								76	19
45		3rd														1	1	1	1	-	1	2	3	1	1	-	2	4	2	2	3	2	-	1	1	-	1	1	-	1	32	13
10		4th																							1	-	-	-	-	-	1	1	1	1	2	-	-	1	-		8	2
2		5th																																	1			1			2	

The Rate of Parasitic Destruction.

We know that the asexual malignant tertian parasite forms 8 to 12 merozoites every 48 hours and is most influenced by quinine. The asexual benign tertian parasite forms 16 to 24 merozoites every 48 hours and is less easily destroyed by quinine. On the other hand, the quartan parasite has the slowest rate of multiplication, 8 to 12 merozoites every 72 hours, and is the most refractory to quinine. This difference in the multiplication-rate is thus not sufficient to explain the difference in cure-rates by quinine, although it undoubtedly plays a part.

In our calculations, if we disregard the occurrence of deaths and the production of gametocytes (i.e., non-multiplying forms), we can consider the rate of multiplication to be a continuous one—that is, 12-fold in malignant tertian and 24-fold in benign tertian infectious every three days. An adult man of 68 kg. body weight possesses about 25,000 billion erythrocytes. Ross, in his enumerative studies, found that in severe infections about 12 per cent. of the erythrocytes were infected with parasites (3000 billion parasites), and when the parasites fell below 250 million (1 parasite in 100,000 erythrocytes) they produced little or no symptoms. Theoretically, a single parasite would be capable in three weeks' time of multiplying sufficiently to produce fever. Every parasite in the body must be destroyed before a complete cure or sterilisation is effected. In latent malaria we know that a large number of parasites can exist in the host and multiply without causing obvious symptoms, but any condition that depresses the vitality of the host can convert the latent malaria into an active disease. As regards the rate of parasitic destruction, we know that a single dose of quinine cannot cure a case of malignant tertian infection, but a series of doses are required extending over a month before a complete cure results. This fact points to the conclusion that the rate of parasitic destruction must be under 100 per cent., otherwise a few intravenous injections of quinine would be sufficient to sterilise every case of this infection. The rate of destruction must be over 95 per cent., otherwise the course of treatment would have to be prolonged for more than a month. Theoretically the rate of parasitic destruction by quinine in malignant tertian infections is about 98 per cent. of each asexual brood. In benign tertian infections, even after a four months' course of quinine treatment (Ross and Thomson), only 50 per cent. of the cases are sterilised.

Quinine in all types of malarial fevers causes an immediate effect on symptoms and a rapid disappearance of parasites from the peripheral blood. Ross considers that this effect is largely due to a reduction in the parasitic population from 3000 billion or more (febrile stage) to 250 million (afebrile). Under these conditions the rate of destruction in benign tertian infections must lie between these two values, 90 and 98 per cent., and the difficulty in sterilisation shows that the rate must be nearer 95 per cent. than 98 per cent.

The cure-rate for a month's course of treatment in this infection varies for the different alkaloids as follows: Quinine 20 per cent., cinchonine about 40 per cent., cinchona febrifuge 50 per cent., cinchonidine and quinidine about 60 per cent.; so that the last two alkaloids must cause a greater percentage destruction of each generation. As the rate of multiplication of the benign tertian parasite is about twice that of the malignant tertian, it follows that in order to destroy every parasite in the body of the host the treatment should extend over six weeks, instead of a month, as for malignant tertian infections.

The Effect of the Total Alkaloids of Cinchona Bark on Benign Tertian Infections.

Cinchona febrifuge is a preparation containing the total alkaloids extracted from cinchona bark, made at the Government factories in India and issued in the form of 3½ gr. tablets. According to MacGilchrist, its average composition is as follows:—

		Per cent.
Crystallisable alkaloids	Cinchonine	18·58
	Cinchonidine	5·84
	Quinine	7·40
	Quinidine	22·83
Non-crystallisable alkaloids	"Quinoidine"	29·12
Moisture, ash, &c.		16·23

The bark, in addition to these alkaloids, contains acids, neutral principles, colouring matter, a trace of volatile oils, gum, starch, and other vegetable matter. The large amount of ash present in cinchona febrifuge is due to the fact that magnesium sulphate is added to the alkaloidal mass to facilitate the preparation of tablets. Cinchona febrifuge was advocated many years ago by Prain owing to its cheapness. We determined to give it a trial, for if it proved to be as efficacious as quinine, its general use would effect a considerable saving in the amount of bark now used to extract quinine. The drug was tested on two series of men. The first series of 53 men were treated for 21 days, with 21 grains given daily by the mouth, the cure-percentage worked out at 50·9. The second series of 57 men were treated as above, but the cinchona febrifuge was only given for 10 days; the cure-percentage worked out at 52·7. Combining these two groups of men (110 individuals) the cure-percentage works out at 51·8. The conclusions we arrived at were as follows:—

(i.) The administration of cinchona febrifuge in benign tertian infections is better than quinine. A three weeks' course gives about the same curative results as a four months' course of quinine (Ross and Thomson's method). The immediate results are also slightly better.

(ii.) The amount of cinchona febrifuge given during a course amounts to 441 gr. and costs 1*s.* 1*d.*, as compared with 1980 gr. of quinine for a four months' course, costing 16*s.* 8*d.* (price in June, 1919).

(iii.) Cinchona febrifuge given in tablet form is more pleasant to take and less toxic than quinine.

(iv.) A considerable saving would be effected in the amount of bark, as the same quantity of bark which yields from 5 to 7 lb. of quinine would give 100 lb. of total alkaloid. This is an important consideration at the present time, when there is a shortage of quinine.

The benign tertian parasite is responsible for about 50 per cent. of the malarial infections in India, and in England, amongst the troops returned from the tropics, it is practically the only malarial infection seen. The employment of cinchona febrifuge in this infection would save the Indian Government approximately 2½ lakhs, or £22,500, annually in drugs, excluding the question of efficiency in men. This result alone should justify the value and need of further research work in the treatment of these malarial fevers.

The Effect of the Cinchona Alkaloids on Benign Tertian Infections.

Fourteen alkaloids have been isolated from the various species of cinchona bark, since Pelletier and Dumas in 1820 first discovered quinine and cinchonine. The names and formulæ of the various alkaloids found in cinchona bark are as follows:—

(A) Crystallisable alkaloids.

Cinchonine and its isomeride $C_{19}H_{22}ON_2$ — Cinchonine and cinchonidine.
Dihydrocinchonines $C_{19}H_{24}ON_2$—Hydrocinchonine, hydrocinchonidine.
Methoxycinchonines $C_{20}H_{24}O_2N_2$—Quinine, quinidine.
Methoxydihydrocinchonines $C_{20}H_{26}O_2N_2$ — Hydroquinine and hydroquinidine.
Alkaloids of the formula $C_{19}H_{24}O_2N_2$—Quinamine and conquinamine.
Alkaloids of the formula $C_{19}H_{18}ON_2\frac{1}{2}H_2O$—Paricine.
Alkaloid of unknown composition—Javanine.

(B) Amorphous alkaloids known as "quinoidine."

Dicinchonine $C_{38}H_{44}O_2N_4$.
Diconquinine $C_{20}H_{46}O_4N_4$.

We can dismiss the amorphous alkaloids from a therapeutic point of view, for we treated a dozen cases with the Laverain remedy (a mixture of quinoidine, arsenic, and picric acid). All these cases relapsed, and some of them had parasites in the peripheral blood during the whole course of treatment. Eight only of the above crystalline alkaloids need be considered, as the others exist merely in minute quantities. These alkaloids can be grouped in two series.

(A) The cinchonine series, which includes cinchonine and its isomeride cinchonidine; and the dihydrocinchonines—hydrocinchonine and hydrocinchonidine.

(B) The quinine or methoxycinchonine series, including quinine and its isomeride quinidine, hydroquinine and its isomeride hydroquinidine.

We can dismiss quinine at once, as only 7·4 per cent. of this alkaloid is present in cinchona febrifuge, and we have seen that this alkaloid produces a low cure rate in benign tertian infections. Cinchonine was tested in 14 patients, of whom eight relapsed. The drug is very toxic and badly tolerated. I had the greatest difficulty in persuading these individuals to continue their treatment for the full three weeks, owing to the intense symptoms of cinchonism. The number of relapses did not justify the employment of this toxic alkaloid for any further trials. The hydro-alkaloids of the quinine and cinchonine series I was unable to obtain, and we were therefore left to test the two alkaloids, quinidine and cinchonidine.

I placed a batch of men on treatment with these two alkaloids. At this important stage of my research I was ordered to the recent Afghan affray. The testing of these alkaloids I therefore entrusted to my co-worker, Assistant-Surgeon Dewey, who has kindly forwarded to me the results obtained.

Quinidine sulphate 10 gr. orally twice a day for 21 days; 62 cases of benign tertian infection treated, of whom 23 relapsed. Cure-percentage 62·9 per cent.

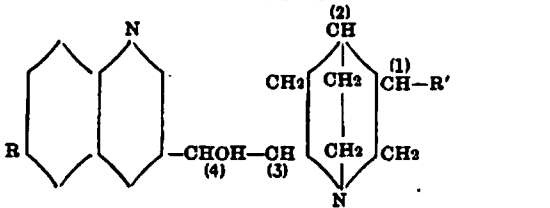
Cinchonidine sulphate 10 gr. orally twice a day for 21 days. Forty-six cases of benign tertian infection treated, of whom

17 relapsed; cure-percentage, 63·1 per cent. As cinchona febrifuge contains 22·8 per cent. of quinidine and 5·84 per cent. of cinchonidine, the efficacy of the total alkaloids is dependent largely upon the quinidine content or the cinchonidine-quinidine mixture. An interesting point is that many have unknowingly used quinidine; for Messrs. Howard, of Ilford, informed me that the bulk of the quinidine they extract is sold for the Eastern market, where, no doubt on account of its cheapness, it is substituted for quinine.

This result of the value of quinidine and cinchonidine at first appeared rather puzzling to me, as my knowledge of the stereo-isomerism of these alkaloids was very limited, and I am deeply grateful to Mr. H. King, M.Sc., of the Medical Research Council's scientific staff, for all the help he has given me on the chemical aspect of this problem.

The Stereo-isomerism of the Cinchona Alkaloids.

The researches of Königs, Skraup, and Rabe have led to the assignment of the following general formula being assigned to these cinchona alkaloids:—



Where R = H in the cinchonine series,
= OCH_3 in the quinine series.
R' = $CH:CH_2$ in the non-hydro-alkaloids,
$CH_2{\cdot}CH_3$ in the hydro-alkaloids.

The alkaloidal molecule consists of two portions—the quinoline nucleus on the left, and the quinuclidine nucleus, more commonly spoken of as the "second half." These two portions are connected by a secondary alcohol group (CHOH). The position of the four asymmetrical carbon atoms are shown, numbered (1) to (4). Each substance of the above formula should therefore have 16 optically active isomerides, 8 of which would of necessity be the enantiomorphous (mirror image) forms of the other 8. The number of those actually known is very small, as the following considerations show. The asymmetry of the carbon atoms (1) and (2) is the same for the four alkaloids, cinchonine, cinchonidine, quinine and quinidine, as on oxidation they all yield the same dextrorotatory compound—meroquinene—in which substance the asymmetry of the carbon atoms at (3) and (4) is destroyed. In agreement with this observation is the fact that β-vinyl-α-quinuclidine-oxime is the same when formed from any of these four alkaloids. A loss of asymmetry of the carbon atom at (4) occurs when these four alkaloids are reduced to dioxy-bases, as the secondary alcohol group (CHOH) is replaced by —CH_2—.

In spite of this loss of asymmetry four different dioxy-basis are formed—viz., cinchotenine, cinchotenidine, quitenine and quitenidine. It follows that the different optical activity of these bases and the four alkaloids is conditioned by the asymmetry of the carbon atom (3). This is further supported by the observation that quinine and quinidine both yield the same dextrorotatory quinotoxin, whilst cinchonine and cinchonidine yield the same dextrorotatory-cinchotoxin. In this case the asymmetry of both carbon atoms at (3) and (4) is destroyed. At present it is not known what part the carbon atom at (4) plays in the optical activity of these alkaloids.

The cinchona alkaloids may therefore be bracketed together in pairs as follows:—

Cinchonine—cinchonidine. Hydrocinchonine—hydrocinchonidine.
Quinine—quinidine. Hydroquinine—hydroquinidine.

The chemical differences between these four groups are as follows. The quinine series are methoxycinchonines—i.e., alkaloids in which H of the cinchonine series has been replaced by a CH_3O group at position 6 in the quinoline ring. The hydro-alkaloids differ from the non-hydro-alkaloids in that the vinyl group ($CH:CH_2$) of the latter has been converted into a $CH_2{\cdot}CH_3$ group. The difference between the members of each pair—e.g., cinchonine and cinchonidine—is due solely to the spatial arrangements of the atoms around the asymmetrical carbon atoms at (3) and (4).

The following table shows the magnitude and signs of the optical activity of the above alkaloids, as base, in alcohol as a solvent.

Alkaloid.	Hydro-alkaloid.	Isomeride.	Hydro-isomeride.
Cinchonine $[\alpha]_D$ + 224·4	Hydrocinchonine $[\alpha]_D$ + 189·8	Cinchonidine $[\alpha]_D$ − 111	Hydrocinchonidine $[\alpha]_D$ − 98·4
Quinine $[\alpha]_D$ − 158·2	Hydroquinine $[\alpha]_D$ − 142·2	Quinidine $[\alpha]_D$ + 243·5	Hydroquinidine. $[\alpha]_D$ + 265·3

Now all of the above crystalline alkaloids which have been tested exert a marked effect on the symptoms, and disappearance of the parasites from the peripheral blood in cases of benign tertian infection, and those I have tested have the same action on the malignant tertian. Again, my co-worker, Dr. Dagmar Curjel, tested the effects of these alkaloids on the hæmoproteus of the pigeon, and found that they had no parasiticidal action. These alkaloids, therefore, show a marked selection for the human malarial parasite, but in different degrees. We have already seen that quinine is a specific for the malignant tertian parasite, and MacGilchrist (1915) considered that hydroquinine was even better than quinine. Our Dagshai results show that quinidine and cinchonidine are more selective for the benign tertian parasite than quinine or cinchonine.

The Factors on which the Parasiticidal Action Depends.

As far as can be reasoned from a chemical study, the parasiticidal action of these cinchona alkaloids is dependent on three factors in the complex alkaloidal molecule.

(i.) The group occupying position 6 in the quinoline ring. Cinchonine is very toxic for man, but the substitution of a methoxy group (CH_3O) in the quinine series decreases the toxicity without materially altering the parasiticidal action. Grimaux and Arnaud have shown that toxicity increases with further increase in the size of the radicle occupying this position.

(ii.) The vinyl group ($CH:CH_2$) in the quinuclidine system. The vinyl group is replaced by a carboxylic group (COOH) in the formation of quitenine and cinchotenine, and Ramsden has found quitenine inert against the malarial parasite. The inactivity may be due to a chemical reaction between an acid and the alkalies of the plasma. The vinyl group is not a decisive factor, as it is present in cinchotoxin and quinotoxin, and both these keto-bases have no parasiticidal action against the malarial parasite. The hydrogenation of the vinyl group ($CH:CH_2$) to $CH_2{\cdot}CH_3$ in the hydro-alkaloids renders such alkaloids more difficult to oxidise, and they are accordingly not easily broken down in the body tissues. This may increase their parasiticidal action. MacGilchrist has shown that hydroquinine has a more potent action than quinine on the malignant tertian parasite.

(iii.) The grouping of the quinuclidine system around the asymmetrical carbon atom at (3), as shown by the optical rotatory power. We have seen that the asymmetrical carbon atoms at (1) and (2) in the cinchonine and quinine series are all similar and therefore need not be considered further. In the formation of cinchotoxin and quinotoxin the asymmetry of the carbon atom at (3) is destroyed and the parasiticidal action is also destroyed. In cinchotenine and quitenine, on the other hand, the asymmetry is still preserved, yet these substances have no therapeutical value. So that the asymmetry of this carbon atom is essential but not decisive.

The lævorotatory alkaloids, quinine and hydroquinine, have a specific action on the malignant tertian parasite, whilst the dextrorotatory alkaloid quinidine (hydroquinidine has not been tested as yet) is more powerful than quinine in its action on the benign tertian parasite. The corresponding lævorotatory isomeride cinchonidine behaves very similarly in its action on the benign tertian parasite. Both these isomerides are much less toxic to man than quinine. We therefore conclude from this chemical study that:

(1) The methoxycinchonines—viz., the quinine series—are less toxic than the cinchonine series.
(2) The hydro-alkaloids are more stable.
(3) That the lævoratory alkaloid quinine is a specific for the malignant tertian parasite, whilst the dextrorotatory alkaloid quinidine is the best alkaloid tested so far for the benign tertian parasite.

Conclusion.

Much more work will have to be done, both chemically and experimentally, before we can gain an idea of the exact action of these alkaloids on the malarial parasites. The work is being continued under the Medical Research Council, and I may here take the opportunity to thank Dr. H. H. Dale, F.R.S., of their staff, for kindly permitting me to work in his laboratory and for the very material help he has given me, both by his advice and by placing the resources of his laboratory at my disposal.

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