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. This statement is peculiarly appropriate 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 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 harmonize 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 Herrington and his even more brilliant interpreters.

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, furthermore, 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 alliance that is of importance to the advancement of medical thought and consequently of medical practice.

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26. Review by Head, Brain, xxxvii., 181, 1925.

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 MALARIAL TERTIAN FEVER.

BY HUGH W. ACOTON, M.R.C.S., L.R.C.P. LOND., major, l.m.s.; /O MALARIAL RESEARCH LABORATORY, BRITISH MALARIAL DIPUT., DAGSHAII, NIGRA HILLS.

The results obtained with the help of my co-workers, Dr. Dagmar Curjel, W.M.S., and Assistant Surgeon J. O. Dewoy, I.M.D., whilst I was in charge of the Malarial Research Laboratory, British Malarial Depot, Dagshaei, Nigra Hills, have 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 method 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. MacGillivray (1913), who made the most systematic trial of the different alkaloids 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 relapse of blood. Yet 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. The discovery of a chemical substance which might be regarded as 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 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 sexual parasites from the peripheral blood. The similarity of a single parasite in the body, or the prevention of relapses, is, however, the only test by which one can truly estimate the complete action of these alkaloids. From the present statistical evidence it is almost impossible to estimate 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 observed much longer than the duration of treatment. Many of the relapses arc not seen by the same medical officer, and in this way too favourable a clinical impression may be created as regards the value.

If the microscope is not sufficiently employed. Fears 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 tertian, and malignant tertian least frequently. This corresponds to our own experience, that the cure-rate produced by quinine in the three types of fever is as 92 per cent. in benign tertian, and 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 the action of the Nervous System.

(1) The exclusion of reinfections amongst our cases during treatment and observation. Dagshaai is situated on
an isolated hill-tow at 6000 feet above sea-level; there are
very few sites suitable for breeding-places for the mosquitoes
and the temperature conditions are, for the greater part
of the year, unfavourable for the fertilisation of the female
gametes.

Every case recorded as a cure was observed for at least two
years and sometimes longer. This observation time-
limited, first suggested by Stephenson, has been applied
every parasitic relapse that occurred amongst our benign
tertian patients and only such relapses numbered 978, and are shown
in the following table.

Table 1 shows the frequency distribution of 978 parametral
relapses due to benign tertian parasites, which occurred during and after treatment, and are shown in intervals of weeks.

<table>
<thead>
<tr>
<th>Interval of weeks</th>
<th>Number of relapses</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>During treatment</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>(A)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 4 5 6 7 8 12 7 8</td>
</tr>
<tr>
<td>(B)</td>
<td>6 12 19 35 130 85 198 99 22 6 1 3 4 5 6 7 8 12 7 8</td>
</tr>
</tbody>
</table>

These results are better depicted in the form of a graph, which is shown below. The two vertical bars divide the curve into three parts. The first part contains the relapses observed during the first six weeks of treatment; the second part contains the relapses observed during the second six weeks of observation; the third part contains the relapses as occurred amongst those cases that stayed longer than two months. The first three-quarters of the curve show a relatively constant level of frequency, while the last quarter shows a more rapid descent. The graph shows that the majority of relapses occur within the first six weeks of treatment, with a smaller number occurring in the second six weeks of observation.

The next section discusses the frequency distribution of relapses in relation to the duration of treatment. The graph shows the distribution of relapses in relation to the number of weeks of observation, with the x-axis representing the number of weeks and the y-axis representing the number of relapses.

An explanation of the absence of malignant tertian infections.

In October, 1918, I took over charge of the Research Laboratory from Professor M. P. Crompton, M.B., 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 rise to the consequent findings. We were not the only ones to observe this absence of the malignant tertian parasite, for it had been noticed by Menard (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 immunologically 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 treatment with quinine before arrival at the depot.
medical history sheets. These men had been treated with quinine at their units in the plains. In Daghali they only received an iron tonic. There were no malignant tertian relapses, 64 relapsed with benign tertian infection, and 33 in 1876. 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 pathologist could have made an error in diagnosing crescents.

(5) In a similar series of 102 different men diagnosed as benign tertian infections these parasities 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 parasity 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 668 cases of this infection treated with quinine there were 24 cases in the first month, 90 cases in the second month, 115 cases in the third month, 76 cases in the fourth month, 190 cases in the fifth month, 118 cases in the sixth month, 74 cases in the seventh month, 70 cases in the eighth month, 60 cases in the ninth month, 45 cases in the tenth month, 32 cases in the eleventh month, and 18 cases in the twelfth month. The cure-rate of quinine in this infection was only 50 per cent.

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

<table>
<thead>
<tr>
<th>Method</th>
<th>No. of cases</th>
<th>Cure rate at</th>
<th>Duration of treatment</th>
<th>Quinine in grams per course</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Intravenous combined with oral</td>
<td>100</td>
<td>18</td>
<td>4 days in 8 weeks</td>
<td>48 to 676</td>
</tr>
<tr>
<td>(B) Intramuscular combined with oral</td>
<td>94</td>
<td>27</td>
<td>6 weeks</td>
<td>1534</td>
</tr>
<tr>
<td>(C) Oral alone</td>
<td>90</td>
<td>18</td>
<td>8</td>
<td>720</td>
</tr>
<tr>
<td>(1) Stephens intermittent 45 gr per day for two consecutive days weekly</td>
<td>113</td>
<td>30</td>
<td>8</td>
<td>480</td>
</tr>
<tr>
<td>(2) Stephens intermittent 30 gr per day for two consecutive days weekly</td>
<td>76</td>
<td>32</td>
<td>16</td>
<td>1560</td>
</tr>
<tr>
<td>(3) Continuous for four months</td>
<td>190</td>
<td>42</td>
<td>10 days</td>
<td>300</td>
</tr>
</tbody>
</table>

Comment.

(1) The duration of the treatment is an important factor in the cure. Bennet found that both in the intravenous (1 to 5 injections) and intramuscular (12 injections) groups, the injections had to be followed by an oral treatment, lasting in 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 impression and caused the fever to subside more rapidly, than when the drug was taken 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 10 days gave a higher cure-percentage than was expected—i.e., 42 per cent. It is possible that the error of chance distribution made this significant result, 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 observers.

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

The malarial population we investigated at Daghali 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 this station. We have already stated that quinine exerts a highly specific action on the malignant tertian parasite, and therefore practically eliminates this parasity from the patient. Under these conditions quinine and benign tertian infections will relapse owing to the failure of quinine and appear again and again amongst a treated population. Quaternary forms a very small proportion of the cases (this infection is relatively rare in the tropics) 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 Daghali 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 time than by giving the long courses of four months that 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 Daghali, 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 168 relapsed. Ninety-five men had further courses after the second course of treatment at Daghali, and 76 relapsed; 45 of these could be followed after the quinate 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 Daghali worked out at 82.5 per cent., 30 per cent., and 25 per cent., respectively, or an average of 34.4 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 parasity 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 two 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.

The table shows what an advantage may be gained by the longer course and the early use of the drug. For this result, it shows that the cure-rate is dependent on some chance factor.
The Rate of Parasite Destruction.

We know that the asexual malignant tertian parasit forms 8 to 13 merosomes every 48 hours and is most influenced by quinine. The asexual benign tertian parasite forms 15 to 24 merosomes every 48 hours and is less easily destroyed by quinine. On the other hand, the quartan parasite has the slowest rate of multiplication of all tertian parasites—that is, 13-fold in malignant tertian and 22-fold in benign tertian infections every 72 hours, and is the most refractory to quinine. The 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., multiplying forms), we can consider the rate of multiplication of tertian parasites—that is, 16-fold in malignant tertian and 24-fold in benign tertian infections every 72 days. An adult man of 58 kg. body weight possesses about 3 billion erythrocytes. Ross, in his enumerative studies, found that in severe infections about 15 per cent. of the erythrocytes were infected with parasites (2000 billion parasites), and when the parasites fell below 250 million (1 billion of 300,000 erythrocytes) they produced little or no symptoms. Theoretically, a single parasite would be capable in three weeks' time of multiplying sufficiently to produce fever. Even if this were the rule, we should be unable to destroy before a complete cure or sterilization is effected. In late malaria we know that a large number of parasites can exist in the body without giving any symptoms, but any condition that depresses the vitality of the host can convert the latent malaria into an active disease.

At the rate of parasitic destruction, we know that a single dose of quinine only gives a case of malignant tertian infection, but a series of doses are required extending into months 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 sterilize every case of this infection. 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 sterilized.

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 300 million (about 100,000 erythrocytes) to 250 million (about 80,000) Under these conditions, the rate of reduction in the parasitic infections must lie between these two values, 98 to 99 per cent., and the difficulty in sterilization shows that the latter figure, not the former, is the accurate one.

The rate for a month's course of treatment in this infection varies for the different alkaloids as follows:

- Quinine—26.6 per cent.
- Cinchonine—40 per cent.
- Cinchonidine—50 per cent.
- Quinidine—about 60 per cent.

The rate of multiplication of the benign tertian parasites is about twice that of the malignant tertian, it follows that in order to sterilize a host of 55 men for malignant tertian infections the treatment should extend over six weeks, instead of a month, as for malignant tertian febrifuge.

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

Cinchona febrifuge is a preparation containing the total alkaloids obtained from cinchona bark, made at the Government factory, in the form of 83 gr. tablets. According to MacGillivray, its average composition is as follows:

- Cinchonine: 18.59
- Cinchonidine: 5.84
- Quinidine: 22.54
- Quinine: 27.25
- Trinucleine: 16.23
- Moisture, ash, &c.: 16.23

The bark, in addition to these alkaloids, contains acids, starch, a trace of volatile oil, gum, starch, and other vegetable matter. The large amount of sah present in cinchona febrifuge is due to the fact that magnesium sulphate is added to the alkaloids to facilitate the preparation of tablets. Cinchona febrifuge was advocated many years ago by Prain owing to its cheapness, and it was given as a trial, for if it proved to be as efficacious as quinine, its general use would affect 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 55 men were treated for 21 days, with 21 grains daily by mouth, the cure-percentage worked out at 50.9. The second series treated as above, but the cinchona febrifuge was only given for 10 days; the cure-percentage worked out at 57.7. By giving these results 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's method).

(ii) The immediate results are also slightly better.

(iii) The amount of cinchona febrifuge given during a certain amount to 641. 3. 1., as compared with 1890 gr. of quinine for a four months' course, costing 16. Ed. (price in June, 1919).

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 quinine, 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 probably the only malarial infection seen. The administra- tion of cinchona febrifuge in this infection would save the Indian Government approximately 23 lakhs, or £22,500 each year. The findings were confirmed in men. This result alone should justify the value and need for 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 X.umann in 1820 first discovered quinine and cinchonine. The names and formulae of the various alkaloids found in cinchona bark are as follows:

(A) Crystallizable alkaloids.
- Cinchonine and its isomeride CoatsHON—Cinchonine and cinchonidine.
- Hydrocinchonine CoatsHON—Hydrocinchonine, hydrocinchonidine.
- Mesochinchonine CoatsHON—Quinina, quinidine.
- Methoxyhydrocinchonine CoatsHON—Hydroquinine and hydroquinidine.
- Alkaloids of the formula CoatsHON—Quinamine and quinacrine.
- Alkaloids of the formula CoatsHON—Paricine.
- Alkaloids of unknown composition—Javanine.

(B) Amorphous alkaloids known as “quinidine.”
- Dihydrocinchonine CoatsHON.
- Dicoquinine CoatsHON.
- Dicoquinine CoatsHON.

We can dismiss the amorphous alkaloids from a theoretical point of view for they treated a dozen cases with the Laveran remedy (a mixture of quinine, cinchonine, and picric acid). All these cases relapsed, and some of them had fever states 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 quinidine 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. Less than 1 per cent. of the alkaloids from whom eight relapsed. The drug is very toxic and is to be tolerated. I had the greatest difficulty in persuading these individuals to continue the treatment after the first few weeks, owing to the intense symptoms of cinchonism. The number of relapses did not justify the employment of this 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, quinine and cinchonine.

I placed a batch of men on treatment with these two alkaloids. At this important stage of my research I was fortunate to the recent introduction of new and strong cinchona alkaloids I therefore entrusted to my co-worker, Assistant-Surgeon Dewey, who has kindly forwarded to me the following reports.

Quinidine sulphate 10 gr. orally twice a day for 21 days; 62 cases of benign tertian infection treated, of whom 23 relapsed. Cure-percentage 65-9 per cent.

Cinchonidine sulphate 10 gr. orally twice a day for 21 days. Forty-six cases of benign tertian infection treated, of whom
If relapse: cure-percentage, 63.1 per cent. As cinchona bark contains 22.3 per cent. of quinine and 5.64 per cent. of cinchonidine, the efficacy of the total alkaloids is dependent largely upon the quinidine content or the cinchonidine. An interesting fact is that many have unknowingly used quinidine, for Messrs. Howard, of Iford, informed me that the bulk of the quinidine is found only for the Eastern market, where, no doubt on account of its cheapness, it is substituted for quinidine.

The result of the value of quinidine and cinchonidine at first appeared rather puzzling to me, as my knowledge of the stereo-isomers of these alkaloids was very limited, and I sought help from Mr. J. R. Backhouse, 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 König, Skraup, and Rabe have led to the assignment of the following general formula being assigned to these cinchona alkaloids:

\[
\begin{align*}
\text{N} & \quad \text{CH} \quad \text{CH} \\
\text{R} & \quad \text{OH} \quad \text{CHR} \\
\text{N} & \quad \text{OH} \quad \text{CHR} \\
\end{align*}
\]

Where \( R = \text{H} \) in the cinchonine series, \( R = \text{OH} \) in the quinine series, and \( R' = \text{CH} \) in the non-quinidine, \( R' = \text{CH}_2 \text{CH}_3 \) in the quinidine, and \( R' = \text{CH}_3 \text{CH}_2 \) in the hydroquinidine.

The alkaloidal molecule is divided into three portions: the quinoline nucleus on the left, the cinchonidine nucleus in the middle, and the non-quinidine nucleus on the right, 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 is shown, numbered (1) to (4). Each substance of the above formulas should therefore, have 16 optically active isomers, 8 of which would of necessity be the enantiomorphs (mirror images) forms of the other 8. The number of these is usually known as a small, as the following considerations show. The asymmetry of the carbon atoms (2) and (3) is the same for the four alkaloids, cinchonine, cinchonidine, quinidine, and quinolinine, as oxidation they all yield the same dextrorotatory compound—merouquine—whereas the basic form of the carbon atom (4) is destroyed. In agreement with this observation is the fact that 8-β-vinyl-a-quinidine-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 quinolinium, as the secondary alcohol group (CHOH) is replaced by —OH.

In spite of this loss of asymmetry four different diastereoisomers are formed viz., cinchonine, cinchonadine, quinidine, and quinolinine. 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 fact that the alkaloids both have the same dextrorotatory quinoline, whilst cinchonine and cinchonidine yield the same dextrorotatory-quinolinine. In this case the asymmetry of both carbon atoms at (3) and (4) is destroyed. As 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, hydroquinidine—hydroquinoline. The chemical differences between these two groups are as follows: the two cinchonine and quinolinine bases and the two hydroquinidine and hydroquinoline bases differ in the sense that one has the carbon atom at (4) reduced to quinolinium, the other at (4) is intact.

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

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Hydro-alkaloid</th>
<th>Isomeride</th>
<th>Hydro-isomeride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinoline</td>
<td>[α] + 154°</td>
<td>Quinidine  [α] + 242°</td>
<td>Hydroquinidine [α] + 293°</td>
</tr>
</tbody>
</table>

Now all of the above crystalline alkaloids which have been tested exact in their action against the parasites from the peripheral blood in cases of benign tertian infection, and those I have mentioned have the same effect. Again, my co-worker, Dr. Dagmar Curjel, tested the effects of these alkaloids on the hemoproteins of the two-Tertian parasites in Rhesus monkeys, where, again, no doubts on account of its cheapness, it is substituted for quinine.

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 melanoid group (CHO) in 6 position increases 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 : CH₂) in the quinoline system. The vinyl group is replaced by a carboxy group (COOH) in the hemoproteins of quinoline and cinchonidine to destroy the parasiticidal action. The hydroxyl group (CH₂OH in the hydroquinidine renders such alkaloids more difficult to oxidize, and they are accordingly no less broken down in the body tissues. This may increase their parasiticidal action. MacGillivray has shown that hydroquinine has a more potent action than quinoline on the malignant tertian parasite.

(iii) The grouping of the quinoline system around the asymmetrical carbon atom at (3), as shown by the optical rotation power. We have seen that the asymmetrical carbon atom at (3) and (4) in the cinchonine and quinoline series are all similar and therefore need not be considered further. In the formation of cinchotin and quinolinine the asymmetry of the carbon atom at (3) is destroyed and the parasiticidal action is also destroyed. In cinchotin and quinolinine the carbon atom at (4) is destroyed and the parasiticidal action is also destroyed. In cinchotin and quinolinine the carbon atom at (4) is destroyed and the parasiticidal action is also destroyed.

The laboratory alkaloids, quinine and hydroquinine, have a specific action on the malignant tertian parasite, which is not exerted on the other and lower races of P. falciparum. The work is being continued under the Medical Research Council, and I may here take the opportunity to thank Dr. H. E. Dale, F.R.S., for their staff, for kindly allowing me to publish this paper. I am under a very material help has been given me, both by his advice and by placing the resources of his laboratory at my disposal.