Privy Council

MEDICAL RESEARCH COUNCIL

CLINICAL COMPARISONS OF QUININE AND QUINIDINE

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COMMITTEE UPON CINCHONA DERIVATIVES AND MALARIA

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[1] See foot-note on p. 5.

CLINICAL COMPARISONS OF QUININE AND QUINIDINE

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I. REPORT OF THE COMMITTEE UPON CINCHONA DERIVATIVES AND MALARIA

A SMALL Committee was appointed by the Medical Research Council in January 1920, with the title of the 'Special Investigation Committee on Cinchona Derivatives and Malaria'. It consisted of Dr. Andrew Balfour (now Director of the London School of Hygiene and Tropical Medicine), Col. S. P. James (late of the Indian Medical Service, and now of the Ministry of Health in London), Major H. W. Acton (Indian Medical Service), and Dr. H. H. Dale (in the service of the Council as Director of the Department of Biochemistry and Pharmacology in the National Institute for Medical Research), acting as Chairman.[1]

The Committee's reference, as its title indicates, was a sufficiently wide one; but the immediate cause of its appointment was the publication by one of its members, Major Acton, of a series of observations on malaria patients, from which he had drawn the conclusion that, while quinine provided a specific cure for infections with the malignant subtertian parasite, it was of less value in eradicating the benign tertian infection, and definitely inferior, in this respect, to other cinchona alkaloids, in particular quinidine and cinchonidine.

The Committee decided to restrict their attention to an endeavour to get further evidence with regard to this suggestion, which, if substantiated, might obviously have an important influence not only on the form in which cinchona alkaloids were made available for general use, but also on the choice of the most suitable species of cinchona for planting. They decided, further, that it would be advisable, in the first instance, to arrange for a simple comparison between the action of quinine and that of one other pure alkaloid from cinchona. Quinidine was chosen for the first comparison, as being the alkaloid of which superiority over quinine, as a remedy for benign tertian malaria, had been most strongly emphasized by Major Acton. In the case of cinchonine, which on account of its relative abundance in various barks might have seemed to be the obvious choice for the first investigation, the Committee were deterred by reports from certain quarters as to its toxicity. Major Acton, in particular, had been obliged to abandon attempts to investigate its curative properties on account of the intense nausea which it produced. Later evidence has suggested that this and other similar experiences may have been due to the use of impure preparations of cinchonine; and, as will be seen later, a pure specimen of this alkaloid is now under trial by one of the authorities who have carried out investigations for the Committee. In the meanwhile, however, for the reasons indicated, the Committee

[1] At an early stage in the Committee's proceedings Major Acton had to return to India, and ceased to be an active member. This Report has been drawn up by the other three members, who must be held responsible for its conclusions.

arranged their programme for the first series of comparative tests with quinine and quinidine. In order to exclude any uncertainty as to the nature and purity of the preparations used, consignments of specially-purified quinine and quinidine bisulphates were obtained from a well-known source (Messrs. Howards), and their purity was carefully checked by determination of their physical constants in the chemical department of the National Institute for Medical Research.

In preparing their programme the Committee found it impracticable to arrange for tests of the relative values of quinine and quinidine in producing a final sterilization of the patient's system from the malarial parasites. Acton's experiments, indeed, had been directed to this point; but he had worked under practically unique conditions, having at his disposal a large number of malarial patients, concentrated under military discipline in a station free from any possibility of reinfection, and kept there until he discharged them as finally cured. On the other hand, the material studied by him had one characteristic which may have influenced the results which he obtained, namely, that it consisted entirely of men who had relapsed after a previous full course of quinine; so that the subsequent cure of a higher proportion by quinidine than by renewed administration of quinine might have another explanation than that of the general superiority of quinidine as a remedy for the benign tertian infection, which Acton advanced. In any case, no such opportunity of treating a long series of patients in a malaria-free district offered itself to the Committee. They were obliged, therefore, to assume that, if this difference between the two alkaloids in final, curative value had a real existence, it should be possible to obtain some indication of it by studying their relative efficacies in causing disappearance of the parasites from the blood during an acute attack. In addition to such a test, an endeavour was made to obtain information as to the relative efficacies of the two alkaloids in preventing relapse by arranging for their supply to out-patients treated for relapsing malaria under the Ministry of Pensions. The results, if obtained, would have been open to the obvious objection that there would be no valid evidence that the doses provided were actually swallowed by the patient, since it was impracticable to arrange for the application of the Tanret or other test. In fact, no results of any kind were obtained from this source, so that a consideration of their value does not arise.

In order to make the comparison a real one, it was considered desirable to lay down a definite programme of treatment, designed to ensure that each patient of two comparable series received one or other of the alkaloids in the same definite dosage, administered by the same technique and at the same intervals. The following is a copy of the Schedule of Suggestions sent to each of the physicians who consented to carry out the comparison :

MEDICAL RESEARCH COUNCIL

CINCHONA DERIVATIVES AND MALARIA COMMITTEE.

Schedule of Suggestions for a Clinical Test of the Relative Therapeutic Value of Quinidine in comparison with Quinine.

1. *Supply of Quinidine and Quinine.*

A sufficient supply of each of the two drugs to be tested will be provided by the Medical Research Council. These will be tested for purity at the National Institute for Medical Research, Hampstead, N.W. 3.

2. *Manner of carrying out Test.*

The conclusion has been reached that the only test on patients likely to give evidence of value is a test of the immediate therapeutic value of the respective alkaloids on patients who are in hospital, and whose blood contains malaria parasites at the time of testing.

The test should be carried out as follows:

(*a*) If possible weigh the patient and calculate the dose on the basis of 10 grains for 70 kilogrammes body weight. If this is impracticable, take 70 kilogrammes as being the average weight of the adult male patient and take 10 grains as the dose. By dissolving in water with a few drops of sulphuric acid make up 10 doses.

(*b*) Arrange to give one dose each morning before breakfast, and each evening before the evening meal. Each time a dose is given take two slides of the patient's blood.

(*c*) Continue the administration and the taking of blood-films until all the 10 doses have been given (5 days).

(*d*) Note carefully the by-effects, such as nausea, albuminuria, &c.

(*e*) The basis of comparison will be the time required for complete disappearance of parasites as judged by examination of the blood-films taken. Such examinations should, if possible, be made on fresh as well as stained films, the same technique being applied throughout, preferably by the same observer. It is suggested that, in order to make the results from different centres strictly comparable, Leishman's stain should, so far as possible, be used in preparing the stained specimens.

(*f*) Alternate patients will be treated with quinine and quinidine respectively, until 50 cases have been treated with each.

(*g*) Complete records of dosage, symptoms, and results to be kept on the special forms provided by the Medical Research Council.

(*h*) The nature of the attack should, so far as possible, be recorded with special regard to the question whether it is:

(*a*) the first attack,
(*b*) a relapse,
(*c*) a new attack in a patient who has previously suffered from malarial infection on one or more occasions.

The nature of previous antimalarial treatment, if any, should also be recorded on the special form.

In order to ensure some uniformity of observation and record, a set of special forms was supplied to each observer, of which a sample is attached (see pp. 14 and 15).

An attempt was made, in the first instance, to arrange for tests in the special malaria hospitals established in connexion with the Ministry of Pensions. For these an additional method of control observation was provided, the officers being requested to take all

blood-slides in connexion with the investigation in duplicate, and to forward one set to the Medical Research Council, who employed an expert protozoologist to furnish separate reports on them. The attempt, after many months' trial, had finally to be abandoned, on account of the lack of suitable clinical material. Such reports as were obtained from this source have value only as furnishing a small body of evidence confirmatory of that obtained from foreign centres.

Meanwhile, by favour of the Colonial Office and the Sudan Government, arrangements were made for confirmative trials to be made in the following centres:

Khartoum,
El-Obeid,
Lagos,
Port of Spain,
Georgetown,
Dar-es-Salaam,
Nairobi,
Entebbe,
Kuala Lumpur.

Colonel Harvey, of the War Office, also arranged for a series of tests to be carried out in Egypt.

It is quite evident that the difficulties of carrying out an exact investigation, on the prescribed lines, and in a tropical centre, are very serious. Most of the supplies of alkaloids and record sheets were sent out over two years ago, but up to the present time only 5 reports have been received. The paucity of records, however, is the less important, on account of the uniformity of the results.

The following is an abstract of the results so far received:

REPORT FROM COL. D. HARVEY (WAR OFFICE, LONDON).

Place of observation—Palestine Hospital, Ludd, Palestine. No. of cases—18. On Quinine—7. On Quinidine—11. Type of infection—all Benign Tertian.

Summary of Results.

1. *Therapeutic effects*, calculated by taking the average number of days from beginning of treatment to disappearance of parasites from peripheral blood.

	Average time of disappearance.
Quinine (7 patients)	3·1 days.
Quinidine (11 patients)	4·4 days.

2. *Toxic reactions.*

	Nausea.	*Vomiting.*	*Buzzing in ears.*	*Blurring of vision.*	*Giddiness.*	*Diarrhoea.*	*Albuminuria.*
Quinine (7)	4	—	3	2	4	—	—
Quinidine (11)	5	4	6	2	7	—	—

It should be noted that the occurrence of vomiting in the earlier stages of treatment in some of the cases under quinidine may have

accounted for the slightly longer average time to disappearance of parasites by rendering absorption of the remedy incomplete.

REPORT FROM THE CIVIL GENERAL HOSPITAL, KHARTOUM.

Total number of cases, 50. Of these 2, in the quinine series, had to be eliminated owing to the fact that parasites were not recorded as present when the treatment began; while another 2, in the quinidine series, had to be eliminated because the trophozoites (subtertian) were still recorded as present at the end of the 5 days' treatment.

1. *Therapeutic effects.*

(a) *Subtertian infections.*	*Average time of disappearance.*
Quinine (15 cases)	4·3 days.
Quinidine (12 cases)	3·8 days.

N.B.—Two patients on quinidine showed parasites at the end of the course. They could not be included in calculating the average, but their existence destroys the significance of any advantage which the figures might be supposed to show for quinidine.

(b) *Benign tertian infections.*	*Average time of disappearance.*
Quinine (9 cases)	3·5 days.
Quinidine (10 cases)	4·6 days.

2. *Toxic reactions.*

	Nausea.	*Vomiting.*	*Buzzing in ears.*	*Blurring of vision.*	*Giddiness.*	*Diarrhœa.*	*Albuminuria.*
Quinine (24)	5	3	4	—	7	4	1
Quinidine (26)	6	4	4	3	6	7	1

REPORT FROM THE PUBLIC HOSPITAL, GEORGETOWN, BRITISH GUIANA.

Total number of cases, 52. In the case of 7 patients the presence of neither trophozoites nor schizonts was recorded. Of the others, 1 patient left hospital before completion of the treatment, 1 died of acute pernicious malaria at an early stage, and 1 on the second day of the record. These 10 cases were eliminated from the analysis, leaving 42 in all, 22 receiving quinine and 20 receiving quinidine.

1. *Therapeutic effects* (average No. of days to freedom from parasites.)

(a) *Subtertian infections.*	*Average time of disappearance.*
Quinine (20 cases)	1·5 days.
Quinidine (16 cases)	1·6 days.

(b) *Benign tertian infections.*	
Quinine (2 cases)	2 days.
Quinidine (4 cases)	2 days.

2. *Toxic reactions.*

	Nausea.	*Vomiting.*	*Buzzing in ears.*	*Blurring of vision.*	*Giddiness.*	*Diarrhœa.*	*Albuminuria.*
Quinine (22)	3	3	8	—	10	—	3
Quinidine (20)	2	2	10	2	14	—	—

Report from the Superintendent Medical Officer, Kampala, Uganda.

The records submitted with this report are not suited to the same method of analysis used for the others. A large proportion of the patients were treated as out-patients, the circumstances having, presumably, made it impossible to carry out the programme suggested by the Committee. A large proportion of the cases, including nearly all those with benign tertian infections, still showed trophozoites at the end of the course of treatment. In these circumstances the comparison must be based on impression rather than on figures. 39 records were submitted, on 31 patients treated with quinidine and 8 with quinine, with the following comments by the Medical Officer:

'(1) Quinidine has a greater effect on S.T. malaria than on B.T. In case of mixed infection, only the B.T. variety was present at the end of the course in the majority of cases.

(2) The B.T. form of malaria appears to be but slightly influenced by either quinidine or quinine in the manner given.

(3) Several patients who professed to be unable to take quinine salts by the mouth were unaffected by quinidine. One patient with a marked reaction to quinine was unable to take quinidine either.'

The following analysis of the results was also kindly supplied with the report:

Results of blood after course of treatment.	*Quinidine. Infection.*			*Quinine. Infection.*		
	S.T.	*B.T.*	*Mixed.*	*S.T.*	*B.T.*	*Mixed.*
Negative	3	1	6			1
Not definite	1	3		1		
Positive to malaria after course		9	6		3	2
Treatment discontinued	1	1			1	
	5	14	12	1	4	3

The most that can be deduced from this report is that quinidine showed no significant difference from quinine, either in therapeutic action or in toxicity for the patient, under these conditions of observation.

Report from the Institute for Medical Research, Kuala Lumpur, Federated Malay States.

This Report, by Dr. William Fletcher, is by far the most complete received by the Committee, and is published *in extenso* on p. 17. Dr. Fletcher had made and published an earlier series of comparisons between quinine and quinidine, each being administered to 20 patients, without detecting any significant difference between their actions. At the Committee's request, and with the pure bisulphates supplied by them, he made a further and larger series of observations, on 70 patients. These were not selected in any way, alternate patients, bearing odd and even numbers, being treated with the preparations supplied by the Committee, and in accordance with the principles suggested in their schedule.

Dr. Fletcher has recorded the disappearance of trophozoites in relation to the number of doses given instead of days of treatment, and it will be convenient to use this notation.

Therapeutic results.

	Average number of doses before absence of trophozoites.
(*a*) Quinine—34 cases.	
Benign tertian (6 cases)	4·5
Subtertian (13 cases)	6·6
Mixed tertian (5 cases)	9·6
Quartan (10 cases)	8·7
(*b*) Quinidine—36 cases.	
Benign tertian (10 cases)	3·4
Subtertian (12 cases)	4·3
Mixed tertian (3 cases)	4·0
Quartan (11 cases)	9·1

It will be seen that, except in the case of the quartan infections, there is some indication of superiority of quinidine over quinine. For Dr. Fletcher's interpretation of his results his own report (p. 26) should be consulted.

With the doses used, Dr. Fletcher observed no significant toxic effects with either quinine or quinidine.

Conclusion.

The conclusion that quinidine is at least as efficacious as quinine is suggested by the results submitted by all the observers. Further, there is no clear evidence of any difference between the two alkaloids in toxicity for the patient. These observations by a number of workers in different parts of the world are confirmatory of the earlier results published by Giemsa and Werner and other authorities. This point, therefore, of the practical equivalence of quinine and quinidine as antimalarial agents may be regarded as definitely settled.

On the other hand, the reports provide no evidence at all in favour of Acton's suggestion that the curative actions of these alkaloids are specifically different for the different kinds of malarial parasite. The reports deal with mixed groups of cases, and there is no indication whatever of a preferential action of quinidine on benign tertian or of quinine on subtertian infections. As already pointed out, Acton's own evidence in favour of these suggestions was, at best, susceptible of alternative interpretations. Quinidine is the cinchona alkaloid which, hitherto, has been most carefully and systematically compared with quinine. It is also, on account of its very close chemical relationship to quinine, from which it apparently differs only in configuration in relation to one of the asymmetric carbon atoms, perhaps the most likely to have a similar therapeutic action in relation to malaria. It does not seem probable that the demonstration of its value would, by itself, have a very important practical effect on planting policy, or on chemical procedure, in relation to the supply of antimalarial alkaloids. The addition of the quinidine yield to the quinine yield would somewhat increase the supply of such alkaloids, but probably not to such an extent as to make a big change in cost of production, or in the relation between supply and demand. The one respect, moreover, in which a definite difference in pharmacological action

between quinine and quinidine is known to exist, viz. in the more potent depressant action of quinidine on heart muscle, which has led to its wide use as a remedy for auricular fibrillation, is not favourable to the use of quinidine in malaria; and although no symptoms related to this aspect of its activity have been noted in the records available to the Committee, it may eventually be found to impose a limit on its use as an antimalarial remedy.[1]

The real importance of the conclusion reached is that it deposes quinine from the position of unique value which practice and tradition have accorded to it among the cinchona alkaloids. A systematic comparison of the other cinchona alkaloids with it, and particularly of cinchonine and cinchonidine, is very much to be desired. It should be noted that Acton's own observations were as favourable to cinchonidine as to quinidine. The trial of cinchonine he abandoned on account of the toxicity of the sample available for his observations.

The Committee have obtained a small supply of carefully purified cinchonine, have had its purity verified by examination in the laboratories of the National Institute at Hampstead, and have placed it in the hands of Dr. William Fletcher, who at present has it under trial at Kuala Lumpur. If cinchonine and cinchonidine should prove also to be equivalent to quinine in antimalarial action, and not significantly more toxic, the problem of the supply of antimalarial alkaloids would be materially changed. It seems hardly probable that a precise equivalence exists in this case, since these alkaloids both differ from quinine and quinidine by the absence of a methoxy-group, being related to one another in the same way as quinine and quinidine are. (It may be noted, incidentally, that there is no real evidence for regarding cinchonine as the relative of quinine, and cinchonidine as that of quinidine, as the terminations might suggest. The only available, though not conclusive, evidence, viz. their optical activity, suggests the reverse relation, cinchonine and quinidine being dextro-rotatory, while cinchonidine and quinine are laevo-rotatory.) But their activity may quite possibly prove to be sufficiently near to that of their methoxy-derivatives (quinine and quinidine) for the difference to be of no real, practical significance. If that should be the case, so that an indefinite mixture of the crystallizable cinchona alkaloids could replace quinine, or any other of them in pure condition, the problem of cheapening the supply of antimalarial remedies would obviously be greatly simplified.

The Medical Research Council's Cinchona Committee are conscious of the fact that the contribution which they have been able to make to this important question is a relatively small one. The carrying out of their programme has been seriously hampered and delayed by the difficulty experienced in finding suitable clinical material close at hand, and in obtaining reports from tropical centres, where the clinical material indeed is abundant, but the conditions for dealing with it are not conducive to systematic observation and record. They are greatly indebted to those medical officers, who, in spite of difficulties, have given their co-operation.

[1] See note on p. 16.

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MALARIA TREATMENT RECORD

Form M R C 145.

Name and address of Hospital ..... Name of Officer in charge of the Case .....

Nature of Attack (*1st Infection, Relapse, or Reinfection*) ..... Nature of previous Antimalarial Treatment, if any .....

Name of Patient ..... Serial Number of the Case ..... Patient's weight on admission ..... *kilogrammes*

Drug selected ..... Dose selected: (1) *Rate per kilo.* ..... (2) *Actual dose* .....

Date.	Serial Number of the Dose.	Amount and Method of Administration.	Time of Administration.	Time of taking Blood Slides.	Temperature of Patient at the same time.	Identification Label of the Slide.	By-effects (*write 'Yes' or 'No' in each column, and if 'Yes' give time of occurrence*).							Other By-effects (*give particulars*).
							Nausea.	Vomiting.	Buzzing in Ears.	Blurring of Vision.	Giddiness.	Diarrhoea.	Albuminuria.	
	1													
	2													
	3													
	4													
	5													
	6													
	7													
	8													
	9													
	10													

This Form, when completed, should be sent to **The Secretary, National Institute for Medical Research, Hampstead, N.W. 3.**

RECORD OF MICROSCOPICAL EXAMINATIONS MADE IN HOSPITAL

This Form, when completed, should be sent to **The Secretary, National Institute for Medical Research, Hampstead, N.W. 3.**

RECORD OF MICROSCOPICAL EXAMINATIONS MADE IN HOSPITAL

	Trophozoites.	Schizonts.	Gametocytes.	Remarks.
Slide made after 1st Dose				
„ „ 2nd „				
„ „ „ 3rd „				
„ „ „ 4th „				
„ „ „ 5th „				
„ „ „ 6th „				
„ „ „ 7th „				
„ „ „ 8th „				
„ „ „ 9th „				
„ „ „ 10th „				

(Signed) .....

Pathologist.

NOTE.

SINCE this report was completed, the Committee have been informed by their former colleague, Major H. W. Acton, that, in a series of somewhat weakly and ill-nourished Indian patients treated by him for malaria with quinidine, he has in several instances observed pronounced depression of the heart's action, which he attributes to the effect of quinidine. Cases of syncope were observed, and there were two cases of sudden death. Since these two patients also suffered from kala-azar, the fatal results could not be with certainty attributed to the quinidine. It seems clear, however, that the effect of quinidine on the heart may constitute a real drawback to its employment.