CINCHONA ALKALOIDS AND BARK IN MALARIA.

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The cinchona alkaloids form one of the most important groups of drugs. Quinin, the chief member of the group, is still the main reliance of the physician in the treatment of malaria, a disease which almost constantly infects 800,000,000 people (Müller) [1], and causes annually about 2,000,000 deaths (Ross) [1]. No cinchona alkaloid, available at present at a cheaper price than quinin, is more effective than the latter in the cure of malaria, but quinidin appears to be its equal, and claims have been made that ethylcuprein and hydroquinin are superior. It has also been claimed that cinchonin and cinchonidin are of antimalarial value equal to quinin, and much evidence has been added tending to prove this for benign tertian fever. In a number of cases of quinin idiosyncrasy the substitution of quinidin has been found to cure the malaria without recurrence of the troublesome side-effects due to the quinin, e.g., urticaria. The study, therefore, of the cinchona alkaloids as a group is of greater interest and value than is suggested by the bald statement of some authors that quinin is the only drug of value in malaria.

The present chief source of cinchona alkaloids is the island of Java. In its elevated regions the Dutch have scientifically cultivated the beautiful blossoming ledgerian variety of an originally Bolivian tree, Cinchona calisaya ("yellow bark"), grafting shoots of this tree upon a hardier stock, Cinchona succirubra ("red bark") which supplies the roots [2]. In the name "ledgeriana" is commemorated that of Mr. Charles Ledger, who, in 1865, shipped from Peru to London a packet of the seeds. The latter were obtained in the Bolivian forests by Mr. Ledger's old Indian servant, Manuel Inca Mamani, whose name even more deserves record in the annals of medicine. He spent four years in the search, for seeds did not ripen every year, and on his return to Bolivia was so ill-treated, for having harmed the industry of the bark-collectors, that he died [3]. All that Mr. Ledger obtained from the sale of the seeds in London, one hundred pounds, he gave to Manuel's widow [4].

The Dutch specialized upon the cultivation particularly of C. calisaya ledgeriana because of the high quinin content of the bark, which they have improved by cultivation and selection. Bark has been obtained, yielding, dried, as high as 13·5 per cent. of quinin alkaloid [2]. This is

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now the principal bark of commerce, and the following figures (Table I) for the average contents of bark worked at Howard’s (London) quinin factory, 1919-1923, probably give a very good picture of the nature of the present supply of cinchona alkaloids. The bark worked was mainly Java ledgeriana [5], the imported bark of world trade. The bracketed figures show Java ledgeriana [6].

**Table I.—Average Alkaloidal Content of Dry Commercial, Mainly Bark of Cinchona Calisaya Ledgeriana.**

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>Average Content</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin alkaloid</td>
<td>4.143% per cent</td>
<td>(4.4-5.1)</td>
</tr>
<tr>
<td>Cinchonidin alkaloid</td>
<td>0.542% per cent</td>
<td>(0.4-0.6)</td>
</tr>
<tr>
<td>Cinchonin alkaloid</td>
<td>0.881% per cent</td>
<td>(0.8-0.4)</td>
</tr>
<tr>
<td>Quinidin alkaloid</td>
<td>0.170% per cent</td>
<td>(0.16-0.2)</td>
</tr>
<tr>
<td>Amorphous alkaloid</td>
<td>0.888% per cent</td>
<td>(0.8-1.6)</td>
</tr>
</tbody>
</table>

It will be seen that in ledger bark, quinidin is the least abundant of the four common alkaloids. It is obtained entirely from the root bark, i.e., probably the *C. succirubra* roots, the stem and branch bark containing usually no quinidin [6]. More abundant sources of quinidin might be other species of cinchona tree, such as *C. officinalis*, but quinidin is not particularly abundant in the bark of any cinchona species. Quinidin sulphate is official in the United States “Pharmacopoeia,” and is principally used in the treatment of auricular fibrillation, where it is five to ten times as effective as quinin, cinchonidin and cinchonin occupying intermediate positions [7].

Cinchonin sulphate is official in the United States “National Formulary.” During a war shortage of quinin it came into considerable use in Italy (1918) and, despite the ominous declarations of certain authors of textbooks, was found no more toxic than quinin, useful in doses of 1-3 grams (15-45 grains) daily, and a great boon in certain cases of quinin idiosyncrasy.

Cinchonidin sulphate is official in the United States “Pharmacopoeia.” Cinchonidin is used to some extent in denaturing alcohol for cosmetic purposes [8]. It has also been used in the treatment of malaria. The writer is informed by manufacturers of quinin that the chief demand for cinchonin and cinchonidin is from some of the makers of popular chill tonics sold in the Southern States. There is abundant evidence that either of these alkaloids will cure malaria, although it has not been proved that they are as active as quinin or quinidin in malignant tertian fever.

Present prices of the sulphates (the cheapest form) of the alkaloids reflect the law of supply and demand, quinidin being most expensive, then quinin and cinchonidin about the same price, and cinchonin cheapest of all.

The amorphous alkaloids (“quinoidin”) of cinchona bark have been tried on numerous occasions in the treatment of malaria and been found rather toxic, with a pronounced tendency to produce nausea, vomiting, diarrhea. Much more important are the cinchona febrifuges, of various origins,
Cinchona Alkaloids and Bark in Malaria

containing mixtures of unseparated crystallizable and amorphous alkaloids as shown in Table II [5, 6]; Waters [5] reported more disagreeable side-effects from febrifuge than from quinin.

<table>
<thead>
<tr>
<th>Alkaloids</th>
<th>Madras, 1923</th>
<th>Bengal, 1922</th>
<th>Javanese</th>
<th>English 1930</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin</td>
<td>8.0</td>
<td>10.5</td>
<td>5.8</td>
<td>11.9</td>
</tr>
<tr>
<td>Cinchonidin</td>
<td>21.0</td>
<td>7.0</td>
<td>12.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Cinchonin</td>
<td>21.0</td>
<td>23.0</td>
<td>20.0</td>
<td>15.3</td>
</tr>
<tr>
<td>Quinidin</td>
<td>4.5</td>
<td>16.0</td>
<td>8.7</td>
<td>4.8</td>
</tr>
<tr>
<td>Amorphous</td>
<td>36.0</td>
<td>33.0</td>
<td>41.3</td>
<td>45.4</td>
</tr>
<tr>
<td>Ash, moisture, &amp;c.</td>
<td>10.5</td>
<td>3.7</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Cinchona febrifuges possess the advantage of cheapness owing to the simplicity of their manufacture from various barks, or from the residues after quinin removal. They are effective. The composition is, however, subject to considerable variation, as may be seen from the table. Mr. Bernard F. Howard [5] has emphasized the grave danger of adulteration by unscrupulous retailers, since only an expert cinchona chemist can make an accurate analysis of cinchona febrifuge, and even then ten days’ work is involved. Similar preparations have been sold under the name of “quinetum,” a name which has also been applied to mixtures of the crystallizable alkaloids, the amorphous being excluded.

The four common crystallizable cinchona alkaloids, as prepared to conform to medicinal (U. S. P. or B. P.) standards are not pure, as shown in the following table [6]:—

<table>
<thead>
<tr>
<th>Alkaloid (or sulphate)</th>
<th>Approximate percentages of impurities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin</td>
<td>Cinchonidin, 2 per cent; hydroquinin, 1 to 3 per cent.</td>
</tr>
<tr>
<td>Quinidin</td>
<td>Hydroquinidin, 6 to 30 per cent.</td>
</tr>
<tr>
<td>Cinchonin</td>
<td>Hydrocinchonin, 10 per cent.</td>
</tr>
<tr>
<td>Cinchonidin</td>
<td>Quinin, 10 per cent; hydrocinchonidin, 8 per cent.</td>
</tr>
</tbody>
</table>

The hydrochlorides and other so-called minor salts may be purer. The quinin sulphate of the German “Pharmacopoeia” (“Deutsches Arzneibuch,” 1926) is stated to be absolutely pure [9]. Commercial quinin formerly often contained the related alkaloid cuprein, from the use of a Remijia pedunculata bark in making quinin, but this bark is not now in any extensive commercial use [9]. It will be seen from the table above that each of the common alkaloids has associated with it a “hydroalkaloid.” The latter differs in each case by the possession of an additional two atoms of hydrogen, converting a \( CH = CH_2 \) group into a —CH_3 —CH_3 group. These hydroalkaloids are prepared by the action of hydrogen in the presence of a catalyst, such as palladium black. The chemical relationships of all the alkaloids which have so far been mentioned,
together with those of a number of others which have been prepared and tried in the search for antiperiodics superior to quinin may be seen from the following formulas and tables.

**GENERAL FORMULA, CINCHONA ALKALOIDS.** The asymmetric carbon atoms are lettered.

**TABLE IV.—Principal Cinchona Alkaloids Tested in Malaria.**

The first alkaloid of each pair is levorotatory, the second its dextrorotatory isomer. Where only one is given, it is levorotatory.

**Cuprein Series,** \( R' = \text{CH}_3 : \text{CH}_2 \).

- \( R = (\text{H}), \text{cinchonidin}, \text{cinchounin}. \)
- \( = \text{OH}, \text{cuprein}. \)
- \( = \text{OCH}_3, \text{quinin}, \text{quinidin}. \)
- \( = \text{OC}_2\text{H}_5, \text{ethyl cuprein}. \)

**Hydrocuprein Series,** \( R' = \text{CH}_2 : \text{CH}_2 \).

- \( R = (\text{H}), \text{hydrocinchonidin}, \text{hydrocinchounin}. \)
- \( = \text{OH}, \text{hydrocuprein}, \text{hydrocupreidin}, \text{neither tested as yet}. \)
- \( = \text{OCH}_3, \text{hydroquinin (methylhydrocuprein), hydroquinidin (methylhydrocupreidin)}. \)

**Aminohydroquinin, NH$_2$ Group at (5).**

- \( = \text{OC}_2\text{H}_5, \text{optochin (ethylhydrocuprein)}. \)
- \( = \text{OC}_3\text{H}_7, \text{cinain (isopropylhydrocuprein)}. \)
- \( = \text{OC}_5\text{H}_{11}, \text{eucupin (isoamylhydrocuprein)}. \)

**Quitenin Series,** \( R = \text{CH}_3\text{O}. \)

- \( R' = \text{COOH}, \text{quitenin}. \)
- \( = \text{COOC}_2\text{H}_5, \text{ethylquitenin}. \)

The optical isomerism in each pair of alkaloids is believed to be due to different spatial arrangements of the atoms around the carbon atom (c), or around carbon atoms (c) and (d) [9][10].

**Value in Malaria of Various Synthetic Relatives of Quinin.**

As might be surmised from the table of the cuprein series of alkaloids (*vide supra*), quinin is methylcuprein. Grimaux [11] showed that it could be prepared by the methylation of cuprein. He further prepared higher homologues, particularly ethyl- and propylcuprein. After these had been tested for toxicity by Laborde [12], they were given a trial in malaria by Bourru [13]. Bourru found that cuprein hydrochlorid interrupted the paroxysms of fever only in doses of 1 gram or more, and that even these doses were not at all reliable; the toxic effects were nil in doses 1-1·5 grams. Ethylcuprein (quinéthylidine) sulphate was administered in five cases of quotidian, one of tertian, one of quartan fever. A dose of 0·5 gram.
Oinchna Alkaloids and Bark in Malaria

(grain viii) usually did not interrupt the succession of paroxysms but 0.75 gram (grain xii) was uniformly successful. The toxic effects were stated as less than with quinin. Propylecuprein (quinopropyl) sulphate was tested in seven cases and found still more effective than ethylcuprein but caused severe cinchonism in all cases in doses of 0.6 gram (grain x), which was not therefore exceeded. Bourru considered that he had proved that ethylcuprein was superior to quinin. But Laveran [13] promptly objected to the method used by Bourru in at least two cases (and Bourru treated only seven with ethylcuprein) in giving the ethylcuprein at a day’s interval after two days’ unsuccessful use of quinin, because, as Laveran pointed out, the quinin might well have modified the condition even if it had not yet terminated the paroxysms. Giemsa and Werner [14] found ethylcuprein (chinathylin) effective, in doses of 0.3-0.4 gram daily, in causing prompt disappearance of parasites and fever and also considered it superior to quinin. The question as to the possible superiority of ethylcuprein over methylecuprein (quinin) is therefore again sub judice. Ethylcuprein would probably be extremely expensive to produce even on a large scale. It is made by ethylation of cuprein. Cuprein must be got from Remijia bark, in which there is not now much trade. Cuprein cannot be got from quinin by demethylating the latter, since this reaction yields an isomer of cuprein, apoquinin, whose constitution appears to be unknown [10].

Baermann [15] tested the antiperiodic activity of a number of alkylhydrocupreins. In preparing these, quinin is hydrogenated to hydroquinin, the latter demethylated to hydrocuprein, and this compound alkylated, resulting in the production of ethyl-, propyl-, isopropyl-, etc., hydrocupreins. He reported the following results, with oral administration:

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Daily dose</th>
<th>Cases</th>
<th>Days treated</th>
<th>Number of parasitic failures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydroquinin (methylhydrocuprein)</td>
<td>0.6-0.8 grm.</td>
<td>6</td>
<td>4-9</td>
<td>1</td>
</tr>
<tr>
<td>Ethylhydrocuprein (optochin)</td>
<td>0.8-1.0</td>
<td>23</td>
<td>3-20</td>
<td>6</td>
</tr>
<tr>
<td>Isopropylhydrocuprein hydrochlorid</td>
<td>0.6-0.8</td>
<td>6</td>
<td>5-8</td>
<td>1</td>
</tr>
<tr>
<td>Isoamylhydrocuprein hydrochlorid or base</td>
<td>0.8-2.0</td>
<td>7</td>
<td>6-7</td>
<td>3</td>
</tr>
</tbody>
</table>

Baermann considered hydroquinin superior to quinin, i.e., effective in smaller dosage, optochin about equal to quinin, the others inferior. Giemsa and Werner [16] also considered hydroquinin superior to quinin, as did MacGilchrist [17], but the statistics published to prove this point are not particularly extensive. Hydroquinin costs considerably more than quinin. Giemsa and Werner [16] considered quinidin (thirty-six cases) and hydroquinidin (thirteen cases) about equal to quinin. Cinchonin and hydrocinchonin they considered useless in doses up to 1 gram (15 grains) a day.
As will be shown later, cinchonin is not useless if the dosage be increased to 2-3 grams (30-45 grains) a day. MacGilchrist [17] found optochin inferior to quinin, cinchonin and quinidin.

Quitenin (see Table IV) is producible by the action of liver pulp on quinin [18]. It appears to be useless in malaria [16], even 30 grains (2 grams) in twenty-four hours [19]. Giemsa [20, 21] considers ethylquitenin as effective as quinin, and seems to regard aminohydroquinin quite as favorably. Quinicin (quinotoxin), an isomer of quinin in which a considerable molecular rearrangement has been produced, appears to be useless [22]. Quinicin is one of the "amorphous" alkaloids of cinchona febrifuge.

Alkaloids producible only by chemical synthesis cannot compete with quinin as antiperiodics unless their higher cost is outweighed by decisive therapeutic advantages. So far none has been definitely proved superior to quinin in any large-scale therapeutic comparison. There remain for consideration those natural alkaloids which cost about the same as quinin or a little less. It is important to examine their title to consideration as antiperiodics, and also interesting to review the history of cinchona bark itself.

**USE OF CINCHONA BARK IN MALARIA.**

It is not certainly known whether or not the Peruvians used cinchona bark in the treatment of intermittent fevers [10]. In 1630 Don Francisco Lopez Canizares, the Spanish corregidor of Loxa, now in Ecuador, is said to have been cured of a fever by the use of the bark [23]. In 1638, hearing of the illness of Ana de Osorio, wife of the Count of Chinchon, Viceroy of Peru, Canizares forwarded to the palace at Lima, 600 miles distant, a parcel of the bark [24]. Her physician, Don Juan De Vega, used it to cure her tertian fever. The next year it was in use in Spain. In 1670 the Jesuits forwarded parcels of bark to the Spanish Jesuit Cardinal Joannes de Lugo at Rome, and, being given away at his palace to the poor, it became known as "Cardinal's bark." In Brussels and Antwerp it received the name "Jesuit powder" because the Jesuits there gave it "without money and without price" to the poor who suffered from quartan fever. In 1669 it cost at Leipzig about 12 shillings ($2.92) an ounce [23], evidently a large sum for those times and probably representing at least a laborer's weekly wage. If the average alkaloidal content of the bark be taken as 5 per cent., and it be assumed that all would be completely extracted by the solvents then used, water or wine, it is clear that 30 grams (approximately an ounce) of the bark would yield about 1·5 grams or 22 grains of alkaloid, or only about enough to control the fever temporarily in each case. Such a conclusion appears in order from the work of Stephens and his collaborators. They have shown that in benign tertian malaria oral administration of quinine sulphate in doses of 10 grains (0·65 gram) on each of two consecutive days causes cessation of febrile paroxysms and effects the temporary
disappearance of all stages of the malarial parasite from the blood [25]. Five-grain (0.3 gram) doses are not adequate. If the dose is made larger, e.g., 30 grains (2 grams), on each of the two days some cases do not relapse, but in one series of eighty-nine cases treated with 90-grain (6 grams) doses, eighty-four cases relapsed in twelve to fifty-three days [26]. A single dose of 120 grains represents approximately the limit of human endurance (collapse, temporary blindness, etc.) and does not obviate relapse [27].

The only species of cinchona bark which appears to have been imported into Europe prior to 1776 was the pale, Crown or Loxa (Loja) bark, of the species miscalled by Linnaeus in 1742 Cinchona (properly Chinchona officinalis) [3]. Analysis of the bark shows about the following proportions of alkaloids:

<table>
<thead>
<tr>
<th>Alkaloids of Cinchona Officinalis Bark [9]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin</td>
</tr>
<tr>
<td>Quinidin</td>
</tr>
<tr>
<td>Cinchonin</td>
</tr>
<tr>
<td>Cinchonidin</td>
</tr>
<tr>
<td>2.77-4.21 per cent.</td>
</tr>
<tr>
<td>0.16-0.32</td>
</tr>
<tr>
<td>0.85-1.37</td>
</tr>
<tr>
<td>0.39-0.65</td>
</tr>
</tbody>
</table>

The Jesuits appear to have adopted the following method of treating intermittent fevers [28]. A quantity corresponding to eight grams of the powdered chinchona bark was given immediately before the paroxysm was expected to begin, and the administration repeated until the patient recovered, the dosage being gradually reduced. Sydenham (1624-1689) started treatment immediately after the termination of the paroxysm and gave thirty-two grams, sometimes in two pounds of red wine, sometimes in “syrup of roses and pinks,” in twelve divided doses at intervals in simple tertian fever of four hours. “Eight or fourteen days later, according to the type of the fever, he repeated the same dose: he likewise recurred several times to the same medication, particularly if the patient had long had the fever, and had suffered in constitution from paludal influence.” Trousseau found this method much more efficacious than that of the Jesuits, and more protective against relapses; vomiting and diarrhoea were, however, likely to occur, necessitating the addition of a little opium. Trousseau preferred “conserve of roses” or syrup of bitter orange as a vehicle for cinchona. The latter is still in occasional use with quinin. While the subject of vehicles is no longer a popular one for instruction in some of our great centres of medical learning, the story goes that it was to the happy discovery of the superior virtues of an infusion of cinchona bark in port wine that Robert Talbor rose to rank and wealth in the days of Sydenham.

“It was under this form that the celebrated empiric Talbor used to administer it in the paroxysm of the intermittents, and so successful was his practice, that Louis XIV was induced to purchase at a large price the secret of his specific; and Charles the Second very unjustly protected him against the power of the College (Royal College of Physicians) and appointed him one of his physicians” [29].
After 1776, perhaps due to beginning exhaustion of the supply of bark near Loxa, other barks began to come on the market, yellow bark, chiefly probably *Cinchona calisaya*, the gray bark of *C. nitida*, and later *C. peruviana* and *C. micrantha*, and the red bark, probably of *C. succirubra*. While the yellow bark, later proved high in quinin content, quickly disputed the greatest popularity with the red and the crown barks, the gray barks, containing little or no quinin, were still considered valuable in the treatment of intermittent fever [30]. The table (VII) shows the proportions of the principal alkaloids in red bark and one of the gray barks.

**Table VII. Alkaloids of C. Succirubra and C. Micrantha Barks [9]**

<table>
<thead>
<tr>
<th></th>
<th>Quinin Quinidin Cinchonin Cinchonidin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red bark—</td>
<td></td>
</tr>
<tr>
<td><em>C. succirubra</em></td>
<td>. . . . 1.38-2.30</td>
</tr>
<tr>
<td><em>C. succirubra</em> (root bark)</td>
<td>. . . . 1.24</td>
</tr>
<tr>
<td>Gray bark—</td>
<td></td>
</tr>
<tr>
<td><em>C. micrantha</em></td>
<td>. . . . Possible trace</td>
</tr>
</tbody>
</table>

**Discovery of the Cinchona Alkaloids.**

Bernardino Antonio Gomez [31], a Portuguese naval surgeon, discovered in 1810 the first of the cinchona alkaloids to be separated from the bark, and named it cinchonin. Pelletier and Caventou [32], in 1820, isolated from yellow bark, quinin, from gray, cinchonin, and from red bark, quinin and cinchonin. Henry and Delondre [33] appear to be entitled to the credit for the discovery of quinidin (1833) although they abandoned their claim in 1834, and "deceived by the analogies between quinidine and quinine," pronounced it merely a "hydrate of quinine." Cinchonidin was discovered by Winckler in 1847 and named by him "quinidin," this name being free. Quinidin was rediscovered in 1849 by van Heyningen and named by him "β quinine." In 1853, "Pasteur, examining different samples of commercial quinidine sulphate, found that they contained two very distinct bases: one identical with the true quinidine of Henry and Delondre and with the β quinine of van Heyningen; the other presenting all the properties of the base discovered by Winckler" and then known also as quinin. "For the first Pasteur kept the name of quinidine, after having established that it had the same composition as quinine, from which it differed in rotating polarized light to the right, instead of to the left as with quinine. The second base, which had the same composition as cinchonine, but was levo-rotatory, he called cinchonidine" [33]. Many authors refused to change the name of Winckler's quinidin to cinchonidin, and the German quinologist Hesse waited till 1873 to make the renunciation. Meanwhile confusion reigned in the nomenclature and troubles the reader of the present day who reviews the records of that time. The state of purity of the alkaloids was much inferior to the present, and in 1870 Clarke [34] said, "There is really very little quinine in general use that is not at present deeply adulterated with cinchonidine." Newton [35] confirmed this by publication of analyses by the New York pharmacist, Rice.
Since the time of Pasteur the existence in cinchona bark of a number of other alkaloids has been demonstrated. Of these the most important are the hydroalkaloids already mentioned. The physiological action of the latter, so far as known, appears to be very much the same as that of the related alkaloids. Thus hydroquinidin, which is a constant and practically irremovable impurity in medicinal quinidin, has, according to Lewis [36], practically the same action as quinidin in auricular fibrillation.

THE CONTROVERSY AS TO THE COMPARATIVE VALUES IN MALARIA OF QUININ, QUINIDIN, CINCHONIN AND CINCHONIDIN.

In 1821, the year following that of the discovery of quinin, Chomel and Double compared the antiperiodic virtues of quinin and cinchonin, and concluded according to Silvestri [37] that cinchonin cures intermittent fever, but slowly and in larger dosage than is necessary with quinin. William Pepper [38], stated, however, that Bally, in 1825, using doses of 6-8 grains of cinchonin sulphate during the intermissions was able to check the fever by about four days of treatment in sixteen tertian, nine quotidian and two quartan fevers. Pepper (1853) used it with "signal success," and considered it equal to quinin. Turner [39] (1864) used it in 100 cases, usually in doses of 3 grains every hour to a total of 20 grains, and said "in slightly larger doses cinchonia is equal as an antiperiodic to quinia." Cinchonin then cost from one-half to one-tenth the price of quinin. Cinchonin still costs less than quinin (1929).

The failure, first of the Spaniards, and later of the South American countries concerned (Colombia, Ecuador, Peru, Bolivia) to restrain the improvident destruction of cinchona trees by the bark collectors, caused other nations anxiety lest the source of quinin should eventually dry up [23]. Various attempts were therefore made to set up the cultivation in other elevated tropical regions. Markham between 1859 and 1879 succeeded in introducing into India all the then-believed commercially valuable species, and about the same time the Java plantations, begun earlier by the Dutch, began to make good progress.

THE MADRAS CINCHONA COMMISSION [40].

When Clements R. Markham had succeeded in establishing in the Nilgiri hills of Southern India the various species of cinchona obtained from South America, it was necessary to decide which tree had best be grown in large numbers as a source of antimalaria alkaloid, since the species differ (Tables I, VI and VII) in the sort of alkaloid which predominates in the bark. The Government of Madras Presidency was advised in 1866 by Dr. Shaw, Medical Inspector-General, to set up a medical commission to test the efficacy of cinchonidin, quinidin, and cinchonin as "cures for fevers," "on a scale sufficiently extensive to secure decisive results." The India office in London acquiesced, and instructed the firm of Howards to
prepare the sulphates of the four alkaloids. The Commission in their report speak of these alkaloids as chemically pure, which they were by the standards of the day. Howards (1929) surmise [6], from their knowledge of the alkaloidal separations then available, that the quinin used was probably free from cinchonidin, but would almost certainly contain hydroquinin; that the quinidin was almost certainly free from quinin, cinchonin and cinchonidin, but might contain anything up to 30 per cent. hydroquinidin as is true to-day with medicinal quinidin sulphate; that the cinchonin probably contained 10 per cent. hydrocinchonin; that the cinchonidin was “heavily contaminated” with quinin, of which it may even now readily contain 10 per cent.

The Madras Chinchona Commission was necessarily hampered by ignorance of the malarial parasite as the cause of malaria, and some of the patients may have been suffering from other fevers. Its work, however, was carried out on so great a number of fever patients, that, even if we consider only those patients who are classified as having suffered from tertian or quartan fevers, and therefore almost surely malarial, we yet have very conclusive evidence from their reports that all four of the alkaloids as tested are of a value in the treatment of malaria comparable to that of quinin. In 1867 they rendered a preliminary report on the treatment “mostly at stations notably malarious” of 1,145 cases of “paroxysmal fevers.” In 1868 they presented the main report on 2,472 further cases, saying “The fevers treated occurred chiefly at stations and in localities known to be malarious, . . . and may, therefore, be considered fevers of the true paroxysmal character caused by malaria.” The results may be summarized as follows:

| Table VIII.—Madras Chinchona Commission—Summary, 1867-68. |
|-----------|-----------|-----------|-----------|-----------|
| Quotidian fever | Remittent fever | Tertian fever | Quartan fever | Total patients treated |
| Quinin | 740 | 5 | 66 | 35 | 846 | 840 or 99·2 per cent. |
| Quinidin | 942 | 8 | 80 | 10 | 1,040 | 1,025 or 98·5 |
| Cinchonidin | 687 | 8 | 63 | 4 | 769 | 745 or 97·7 |
| Cinchonin | 872 | 6 | 86 | 5 | 969 | 946 or 97·6 |

The criterion of cure was “cessation of febrile paroxysms,” which may, of course, occur without complete disappearance of malarial parasites from the blood.

The dose varied from 2 to 20 grains (quinin and cinchonidin), 2 to 30 grains (quinidin and cinchonin). The frequency of administration also varied. No treatment appears to have lasted longer than sixteen days.

The Commission ranked quinin and quinidin as of “equal febrifuge power,” cinchonidin “only slightly less efficacious,” cinchonin “considerably inferior to the other alkaloids” but “notwithstanding a valuable remedial agent in fever.” Since the failures with any of the alkaloids might have been due to wrong diagnosis, or to insufficient dosage or
duration of treatment, their occurrence in greater number with cinchonin and cinchonidin might well have been a matter of chance.

The Commission obtained its published results by compilation of reports from twenty-six medical officers and subordinates, working in various localities considered malarious. Analysis of the report shows that certain reports might well be eliminated, e.g., that of one observer who, though he reported on two hundred cases, treated all with quinin. If we eliminate also all reports in which only two alkaloids were tried by the observer and those in which the report made on any alkaloid, except quinin, includes less than ten cases, we have left the most valuable part of the report, the work of nine observers on 2,717 cases out of a total of 3,617. Their results are presented in the table (IX), the localities in which they worked being

**Table IX.—Summary of Reports of the Nine Chief Observers of the Madras Chinchona Commission, 1867-1868.**

<table>
<thead>
<tr>
<th>Name</th>
<th>Localities</th>
<th>Quinin</th>
<th>Quinitin</th>
<th>Cinchonin</th>
<th>Cinchonidin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Cleveland</td>
<td>Mysore..</td>
<td>33</td>
<td>0</td>
<td>43</td>
<td>1</td>
<td>114</td>
</tr>
<tr>
<td>Dr. J. Dougall</td>
<td>Northern Circ.</td>
<td>23</td>
<td>1</td>
<td>24</td>
<td>0</td>
<td>71</td>
</tr>
<tr>
<td>Dr. J. Fitzgerald</td>
<td>Labuan</td>
<td>36</td>
<td>0</td>
<td>109</td>
<td>8</td>
<td>316</td>
</tr>
<tr>
<td>Dr. Foy</td>
<td>Sumbulpore</td>
<td>43</td>
<td>0</td>
<td>98</td>
<td>0</td>
<td>39</td>
</tr>
<tr>
<td>Dr. J. M. Houston</td>
<td>Doomagoodom.</td>
<td>71</td>
<td>1</td>
<td>69</td>
<td>0</td>
<td>297</td>
</tr>
<tr>
<td>Dr. J. Keess and Asst. Apothecary M. Wade</td>
<td>Goodaloor (Wynaad)</td>
<td>807</td>
<td>1</td>
<td>416</td>
<td>2</td>
<td>447</td>
</tr>
<tr>
<td>Dr. D. J. McCarthy</td>
<td>Cochin</td>
<td>38</td>
<td>0</td>
<td>34</td>
<td>1</td>
<td>154</td>
</tr>
<tr>
<td>Dr. G. E. Whitton</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>452</td>
<td>2</td>
<td>748</td>
<td>5</td>
<td>2,692</td>
</tr>
</tbody>
</table>

Percentage cured

|              | 99.5% | 99.3% | 98.7% | 98.9% | 99.0% |

given for reference. The reports of Keess and Wade, who worked at first together, are presented as one.

The table shows that these nine observers, with the exception of Fitzgerald, found but little difference in the antiperiodic power of the four alkaloids. Of Fitzgerald's eleven failures the Commission says "it is observed that in ten of these cases the paroxysms were checked by two and three 6-grain doses of quinine, and in one by two 12-grain doses of chemically pure quinine, by which the superior efficacy of quinine is evidently implied. It is necessary, however, to note that the fever-patients at Labuan were invariably given only a single 8 or 6-grain dose a few hours before the expected paroxysm, which we think can scarcely be deemed a quantity sufficient to check in every instance recurring febrile attacks of a paroxysmal nature."
The table also shows that Keess and Wade together treated over forty per cent. of the cases reported on, 1,541 out of 3,617. The Commission printed the brief report of each of these two in full, and they are here reproduced, because of the clinical details included.

**Report on the Chinchona Alkaloids (to the Madras Commission, 1867).**

(By J. Keess, M.D., M.R.C.P.L.)

1. In obedience to instructions received from the head of the medical department, I proceeded to Goodaloor, South-east Wynaad, and started the alkaloids experiment on the 1st of June, 1866.

2. When I arrived at Goodaloor, fever was prevailing to a great extent, both there and in the adjoining coffee estates. Owing to the great rush of fever subjects to the dispensary, I decided on first observing the effects of large doses of the alkaloids.

3. As there were many persons suffering from fever in June, the administration of a single large dose enabled me to take up a larger number of cases than I would have been able to do had I begun with small and repeated doses.

4. I first tried chinchonidine, in doses varying from 10 to 15 grains, and in a few days I was pleased to find that it acted as quinine would have done in similar doses.

5. I next tried quinidine with similar results.

6. I left chinchonine to the last, as it was said to be an irritant of the gastro-intestinal mucous surface. I was, however, agreeably disappointed when I found that it did not cause nausea or vomiting in doses of 10 grains, and that it was as good an anti-periodic as the sister alkaloids.

7. Encouraged by the absence of symptoms indicating gastro-intestinal irritation, I used chinchonine in fever complicated with diarrhoea, and I am satisfied that it is not an irritant of the stomach or bowels, any more than quinine is, in certain cases.

8. Some of my patients were out- and in-patients of the Goodaloor dispensary. Others were visited in the bazaar, and in the adjoining coffee estates, from two to six miles distant from Goodaloor.

9. The great majority of my patients were half-starved emaciated persons, with flabby muscles, dry, dirty, and shrivelled skins, large spleens, bloodless eyes and tongue, and small atonic pulse. In many of them languor was so marked that they could with difficulty muster up energy enough to reply to questions; and so prostrated were some of them, that they were with difficulty induced to take the medicines offered to them.

10. I have not attempted to reduce to a small compass the results set forth in the tabular reports, as I hear that this work has been undertaken by the Chinchona Commission, but I beg leave to point out that a 10-grain
dose of all three alkaloids seemed sufficient to check the return of fever in the majority of cases. Where it failed to check the return of fever, the succeeding paroxysm was generally observed to be less severe. When the paroxysms returned with unabated severity, 15 grains, and then 20 grains were tried. In a few severe cases I administered, at the onset, 15 or 20 grains.

11. During the four months that I was employed in the Wynaad, 467 cases were treated with the alkaloids. The majority of these cases were of the quotidian type. Bronchitis, congestion of the lungs, pneumonia, diarrhoea, dysentery, and anasarca were occasional complications. I may as well add, that these complications did not in the least interfere with the administration of the alkaloids. Where the local affection required special attention, the alkaloids were given with remedies suitable to the complication. I may here add, that all three alkaloids appeared to be as efficacious as quinine.

* * * *

(signed) J. Keess, M.D., Assistant Surgeon, Late on Special Duty in the Wynaad.

Madras, 25 February, 1867.

Wade's Report on 1,079 Cases, to the Madras Commission, 1868.

1. In forwarding the accompanying two tabulated sheets for the month of December, 1867, I beg to state that, in accordance with your instructions conveyed in Memorandum, No. 4591, the experiments with the alkaloids ceased on the 19th instant, owing to the last supply having been expended, and the report on its therapeutic properties as an anti-periodic is now submitted.

2. In the latter part of September, 1866, Assistant Surgeon J. Keess, who was specially employed on this duty, was removed to Madras. During the four months the experiments were carried on previous to his departure, the results proved so satisfactory that I was induced to continue them.

3. Since then, 1079 cases have been treated by these salts with success, as is shown in the accompanying general tabular statement.

4. Disulphate of Quinine (chemically pure).—The experiments connected with this salt are of a later date than the other alkaloids, having been put into practice in March last. The increase of the number treated over that of chinchonidine and chinchonine may be attributable to the fact that not only at the time of its introduction were paroxysmal fevers very prevalent, but its use was continued for a longer number of days monthly than the two above-named alkaloids. Out of 284 cases thus treated, one dose was sufficient to stay the attack of fever in 251 cases, while 32 required a second dose, and one solitary case complicated with congestion of left lung required the administration of a fourth dose.

5. Quinidine.—With this salt 300 cases have been treated, of which number one dose was sufficient in 268 cases, while 30 required a second
dose, and only two a third dose, so as to effectually stay the attack of fever. It exactly, not unlike quinine, dissolves with dilute sulphuric acid, and is very similar in its effects to that drug, if not equal to it.

6. Chinchonidine.—With this preparation 242 cases have been treated, one dose being sufficient in 219, while 21 had a second dose, and two a third dose. It, to some extent, creates nausea, and even induced vomiting in a few cases, leaving a disagreeable sensation for some time afterwards; nevertheless, its properties as an anti-periodic can be depended upon.

7. Chinchonine.—This salt was at first carefully and cautiously used, as I was led to believe that it was an irritant of the stomach and bowels, and though in a few cases vomiting was induced, and in others diarrhoea (doubtless quinine acting likewise in similar cases), yet its use proves that it is not a gastro-intestinal irritant. It has, in common with the other alkaloids, been used in cases complicated with diarrhoea and dysentery, in combination with laudanum, successfully: 253 cases were thus treated, 215 requiring one dose for their cure, while in 38 a second dose was administered.

8. Decoction of Bark was prepared with the dried leaves, twigs and bark of the chinchona plant as supplied by the superintendent of the Government Chinchona Plantation. It was continued for a couple of months only. Twenty-two cases were thus treated, in 20 of whom the attack was stayed, whilst in two it failed, quinine being resorted to. Of the two failures, one case of a month's duration, complicated with anasarca and general debility, may not be surprising; but the other, which was a mild attack and of short duration, yet derived no apparent benefit from the decoction, though it was steadily continued for five days. The dose usually administered was four ounces three times a day, and though the alkaloids effect a more speedy cure, which perhaps is more desirable with a working population, yet this simple anti-periodic can be obtained by the possessors of a few chinchona plants.

9. Chinchonine (cinchonism ?) was very generally complained of by the patients treated with the alkaloids, but it was apparent that it was more readily induced by the chemically pure disulphate of quinine and quinidine than by chinchonidine and chinconine.

10. The alkaloids, not unlike quinine, have a tonic effect, helping digestion and increase of appetite.

11. The majority of the cases were out-patients of this dispensary, they were bad specimens for experimental purposes, many being half-starved and emaciated, generally with enlarged spleens, a small weak pulse, invariably anaemic, and with marked pulsation.

12. Of the number treated, 87 were in-patients of this dispensary, and though they were for some time afterwards under treatment, either for other diseases or observation, they continued to remain free from fever while in hospital. Of the remaining number treated as out-patients, many were free from attacks, for long periods, enjoying good health, whilst many
again returned to the dispensary after the elapse of weeks for treatment for a second attack; but I submit that their return should be regarded more as a necessary consequence attributable to a continued residence in a notably malarious climate, than to the inefficiency of the salts to stay the attack.

13. The alkaloids were generally administered in 10-grain doses dissolved in water—quinine and quinidine being soluble, chinchonidine and chinchonine partially so—each dose being invariably taken in my presence.

14. In conclusion, I would beg to state that, after a trial of 19 months with these salts in a malarious district, where paroxysmal fevers are very prevalent, a 10-grain dose of any of the alkaloids, as was usually given, tends either to cut short the attack of fever for some time, or mitigates markedly the severity of another paroxysm.

Even the most cursory examination of these reports of the Madras Chinchona Commission is sufficient to remove any doubt that quinidin, chinchonin and chinchonidin (used like quinin) will terminate, except perhaps in a few instances, the febrile paroxysms of malaria as well as quinin. This report, however, received little circulation, being printed in an unwieldy government bluebook along with a mass of other information, chiefly regarding the chinchona plantations in India. Dougall [41] published a separate report on his seventy-two cases, but apart from this and brief mention in a few publications, the work has since dropped from sight so that only a few medical texts now even acknowledge its having been done, despite the considerable practical importance of the subject. Lauder Brunton [42] in 1885 said "The other cinchona alkaloids . . ., as also quinine, may be used as prophylactics in order to prevent the recurrence of ague in persons travelling through or living in malarious districts as well as for the purpose of curing malarious conditions already present."

Recent Comparisons of Quinin, Quinidin, Cinchonin and Chinchonidin.

Following the discovery of the malarial parasite, and the separation of malaria into simple (benign) tertian, malignant (tropical, aestivo-autumnal) tertian, and quartan fevers, further comparisons of the value of the alkaloids in the different types of malarial fever were naturally indicated, but it is only in comparatively recent years that these have been begun. They are not yet complete.

Some Early Observations.—Giemsa and Werner [14], using quinidin hydrochlorid in doses of 0·2 gram (3 grains) twice a day, found it to cause disappearance of malarial parasites in three days, and of the fever even more quickly. They found cinchonin hydrochlorid in doses of 0·2 gram
five times a day ineffective, but MacGilchrist [17] (1915) considered cinchonin most effective of the common cinchonin alkaloids. He carried out clinical investigation on adult male prisoners in two jails at Alipore in India. All were sick, and on examination showed the malarial parasite in the peripheral blood. Every eight hours a dose of the drug being tested was given in solution and a blood smear made for parasites. In a first series of seventy-two cases quinin, quinidin, cinchonidin and cinchonin sulphates were given in doses of 1 gram per 70 kilograms body weight or approximately 1 grain per 10 pounds body weight, or for a 150-pound man, 15 grains three times a day. Nine such consecutive doses were adequate in all cases, and with any of the four alkaloids, to cause disappearance of asexual parasites from the peripheral blood. Only two of the cases were quartan infections; in these the ninth dose was required to clear the blood, one treated with quinin being clear thirty-six hours after the ninth dose, and one treated with cinchonin being clear twenty-four hours after the ninth dose. It was difficult from this series to determine any advantage of one alkaloid over another.

In two further series MacGilchrist attempted to compare the rapidity of action of various cinchona alkaloids on the asexual parasites in very small doses proportioned to body weight. In this final series no drug appears to have been used in more than thirteen patients. He ranked the common alkaloids in order of effectiveness, the best first, cinchonin, quinin, quinidin (cinchonidin was tried on only three patients). But cinchonin sulphate, which he used, contains about 7 per cent. more alkaloid than quinin sulphate, and about 10 per cent. more molecules per gram weight. Hydroquinin hydrochlorid, which he considered even better than cinchonin, may also contain somewhat more alkaloid than quinin sulphate. His results hold good only on the basis that all these salts have the same percentage of alkaloid. In summary, he showed that all the common cinchona alkaloids are effective in clearing the peripheral blood of malarial parasites, as well as in subduing the fever, which latter had been proved by the Madras Commission.

Two patients were used as controls and received no antimalarial treatment; one of these, a sufferer from malignant tertian fever, got well in four days, a “spontaneous cure.” MacGilchrist says, “This case is of importance in showing that the therapeutic value of these alkaloids cannot be gauged from one or two experiments only, as the protective forces of the patient occasionally aid the alkaloid greatly in its therapeutic effect.” Such spontaneous cures (without treatment) have been noted by Yorke and MacFie [43].

Observations in Italy.—During the general upset of international commercial relations consequent upon the 1914-1918 struggle, the Italians found themselves for a time rather short of quinin, and turned to cinchonin particularly as a quinin substitute. Bini [44] describes an antimalarial campaign in which cinchonin sulphate was substituted for
Cinchona Alkaloids and Bark in Malaria

nearly 40 per cent. of the total alkaloid, quinin forming the remainder. The results were good. Pontano [45] and Sanguinetti [46] considered cinchonin particularly valuable in cases where quinin could not be tolerated because of idiosyncrasy. As far as the general malaria problem was concerned, most appeared to consider cinchonin reliable in benign tertian and perhaps quartan fever, but not so good as quinin in malignant tertian fever. Sanguinetti [46], using Dionisi’s scheme of quinin treatment, 6 x 1·6, 14 x 0·8, 60 x 0·4, where the first figure is days of treatment, the second dose in grams (1 gram = 15·6 grains), obtained in twelve soldiers cessation of fever with cinchonin treatment and no reappearance for twenty to twenty six days. All had benign tertian malaria. Silvestri [37] reviewed the literature on treatment of malaria, and stated that he had treated numerous cases of both benign and malignant tertian fever with cinchonin sulphate. He reported fourteen cases in detail. Amantea [47] reported good results in twenty-four cases treated with cinchonin, including all three types of malarial fever. He used two grams (30 grains) of cinchonin sulphate a day for as long as seventeen days without harm and found the drug well tolerated. Filipella [48] reported on twenty-three cases, using cinchonin in doses of 1 to 2·5 grams a day; he considered the remedy equal to quinin in benign tertian fever, but inferior to quinin in malignant tertian. Fiorentini [49] reported observations on the treatment of malaria in twelve children with cinchonin; he used as high as 0·5 gram (8 grains) in one day in a child of three and one-half months, 1·5 grams (23 grains) in a child of thirteen months. Such doses appear rather large in view of the adult daily dose of 1 to 3 grams. Fiorentini also found cinchonin easy to administer. Lega [50] has more recently (1928) compared cinchonin and quinidin. Using cinchonin sulphate in fifteen cases and quinidin sulphate in thirteen cases of benign tertian malaria he found the two of approximately equal value in terminating the fever and removing the parasites from the blood; the daily dose was 1 gram (15 grains) in each case. Using cinchonin in fifty-three cases and quinidin in twenty-seven cases of malignant tertian fever he found quinidin very reliable but cinchonin rather inferior; the daily dosage of quinidin sulphate was 1·5 grains (23 grains), and cinchonin sulphate had to be used in doses of at least 2 grams (30 grains) daily for good results, and even 2·5 to 3 grams (38 to 46 grains) was not always successful.

Observations in India.—Acton [51, 52] carried out observations at Dagshai Malarial Convalescent Depot (near Simla, N. India) a place 6,000 feet above sea level, where the possibility of reinfection was practically absent. The cases reported as “cured” showed no relapse within two months following cessation of treatment. Stephens [53] has found relapse to occur even four months after blood had become “negative” as a result of quinin treatment. The patients were British soldiers. Very few had malignant tertian malaria. All had previous quinin treatment. Acton considers a single course of quinin more likely to be effective in malignant tertian than in benign tertian malaria.
The principal results are shown in the table.

**Table X.—Cinchona Alkaloids and Febrifuge in Chronic Benign Tertian Fever**
(ACTON, 1920), cf. Table XI.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treated</th>
<th>Cured</th>
<th>Plan of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin (usually sulphate)</td>
<td>663</td>
<td>18-52.6 per cent.</td>
<td>Various, best by prolonged (4 months' oral treatment, 30 gr. a day for 10 days followed by iron and arsenic tonic for three weeks.</td>
</tr>
<tr>
<td>Quinidin sulphate</td>
<td>190</td>
<td>42.1</td>
<td>10 gr. (0.6 gr. ) twice a day for 21 days.</td>
</tr>
<tr>
<td>Cinchonidin sulphate</td>
<td>46</td>
<td>65.9</td>
<td>As with quinidin.</td>
</tr>
<tr>
<td>Cinchonin</td>
<td>14</td>
<td>42.8</td>
<td>Not stated.</td>
</tr>
<tr>
<td>Cinchona febrifuge</td>
<td>110</td>
<td>51.8</td>
<td>21 gr. a day for 10 days (55), for 21 days (55).</td>
</tr>
</tbody>
</table>

These results have been widely quoted as showing a considerable superiority of quinidin over quinin in the treatment of benign tertian malaria. Later work has failed to support this conclusion.

Acton observed that patients relapsing have as good a chance of recovery on the next course of quinin as on the preceding course and are eventually cured.

Acton considered quinidin superior to quinin in benign tertian malaria. Sinton and Bird [54], however, were unable to confirm this. Following five years' work with 1,300 patients they say, "The four chief alkaloids showed almost an equal value in preventing relapse in chronic benign tertian malaria." The following, selected from their results for comparison of the effects of the alkaloids, bring out this point, and also show that the longer course of quinin gave better results. Their criterion of cure was absence of parasites in blood samples taken every week for eight weeks following cessation of all treatment.

**Table XI.—Cinchona Alkaloids and Febrifuge in Chronic Benign Tertian Fever**
(SINTON AND BIRD, 1929), cf. Table X.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment</th>
<th>Treated</th>
<th>Cured *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quinin sulphate</td>
<td>Various</td>
<td>601</td>
<td>30.6 per cent.</td>
</tr>
<tr>
<td></td>
<td>30 × 14; 10 × 42</td>
<td>105</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>30 × 14; 20 × 7</td>
<td>73</td>
<td>30.6</td>
</tr>
<tr>
<td>Quinidin sulphate</td>
<td>Various</td>
<td>194</td>
<td>15.5</td>
</tr>
<tr>
<td></td>
<td>20 × 28</td>
<td>16</td>
<td>31.3</td>
</tr>
<tr>
<td>Cinchonin sulphate</td>
<td>20 × 28</td>
<td>69</td>
<td>31.9</td>
</tr>
<tr>
<td>Cinchonidin sulphate</td>
<td>20 × 23</td>
<td>73</td>
<td>30.6</td>
</tr>
<tr>
<td>Cinchona febrifuge</td>
<td>20 × 21</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>30 × 7; 20 × 21</td>
<td>67</td>
<td>25.4</td>
</tr>
</tbody>
</table>

* Patients treated apparently successfully but not kept under observation would considerably raise this result. All such cases omitted from above table.

† 30 × 14; 10 × 42 means 30 gr. a day for 14 days followed by 10 gr. a day for 42 days.

The results of Sinton and Bird appear to dispose of Acton's idea that quinidin is preferable to quinin in benign tertian fever. In similar dosage and duration of administration all of the alkaloids appear to have the same efficiency. The results with quinin are evidently improved by prolonging the period of ingestion of small doses. It is unfortunate that this was not also done with the other alkaloids for comparison. No superiority of
chinchona febrifuge is demonstrated. Its composition is quite variable
(Table II).

The OuyameZ Campaign.—The desirability of a more lengthy administra-
tion rather than huge dosage of alkaloid in malaria can be seen from
Barlow's [55] figures for the results of an antimalarial campaign in the
coastal plains of Honduras, in which the New Orleans malariologist, Dr. C.
C. Bass, was consultant. Barlow used 5 grain (0.3 gram) capsules of quinin
bisulphate which contains about 60 per cent. of quinin. Following a
preliminary laxative he gave 20-30 grains a day (1.3-2 grams) for two or
three days, 15 grains daily (1 gram) for one month, then 15 grains twice a
week for two months more. Five hundred and eighty of his patients could
be watched for three to six months after treatment was concluded.
Reinfection could not be excluded. The results were, however, good:—

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Duration of treatment</th>
<th>Relapses</th>
<th>Percentage cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>116</td>
<td>Less than one month</td>
<td>116</td>
<td>0 per cent</td>
</tr>
<tr>
<td>245</td>
<td>One month</td>
<td>91</td>
<td>63 &quot;</td>
</tr>
<tr>
<td>218</td>
<td>Three months</td>
<td>0</td>
<td>100 &quot;</td>
</tr>
</tbody>
</table>

Observations in Malaya.—William Fletcher [56] of the Institute for
Medical Research of Kuala Lumpur, Federated Malay States, has recently
published a very valuable work which is a mine of information for anyone
interested in the treatment of malaria. He reviews carefully the use and
abuse of quinin by all methods of administration and gives his own acute
personal observations. Fletcher has also made comparisons of the action
of the four main cinchona alkaloids on the fever and the parasites
in malaria, working with all three types of malaria.

No brief summary will be attempted of Fletcher's work, but some of
his conclusions may be briefly given. He states, "In doses of ten grains
twice a day, the four crystallizable alkaloids, quinine, quinidine, cinchonine
and cinchonidine, appeared to be of equal value in bringing about the
disappearance of malaria parasites, in patients weighing about 100 lb.
None of these alkaloids produced toxic symptoms when they were
administered in this quantity. In small doses of five grains a day, cinchonine
did not appear to be quite so potent as the sulphates of quinine and
quinidine. Cinchonidine sulphate was definitely inferior to the other
crystallizable alkaloids, when given in small doses. The results of quinidine
sulphate in quartan malaria were slightly better than those of quinine
sulphate. Quinoidine, in doses of five grains a day, did not cause the
disappearance of malaria parasites from the blood. Ten-grain doses are
too toxic to be employed in the treatment of malaria."

Because of the allegation that cinchonin was poisonous Fletcher made a
special investigation of its action on twenty-five patients with tertian,
subtertian fever or mixed tertian fever. He says, "Cinchonine did not
cause any unpleasant symptoms when it was given at the rate of 0.1 grain per pound (about 10 grains): if anything, it proved slightly less toxic than quinine. Five of the patients were vomiting occasionally when they began to take the drug, but the vomiting ceased after a day’s treatment. Three patients had slight diarrhoea. One man had albuminuria when he came into the hospital, but it disappeared after he had been taking cinchonine for four days.” An average dose of 20 grains (1.3 grams) twice daily to men weighing about 100 pounds caused giddiness. “One vomited and one complained of his sight, but the symptoms were certainly no worse than they would have been with quinine.”

**Substitution of Other Cinchona Alkaloids in Cases of Quinin Idiosyncrasy.**

A small number of cases are on record of patients who were unable to take quinin because it produced urticaria, dyspnœa, dermatitis, hemoglobinuria, etc., but were able to take quinidin or cinchonin. Giemsa and Werner [14] reported the successful substitution of quinidin. Dawson and Garbade [57] have recently reported a case of idiosyncrasy to seven levo-rotatory cinchona alkaloids, including quinin, cinchonidin, optochin, but not extending to the dextrorotatory isomers, quinidin, cinchonin, optochidin, etc. Fletcher [56], Fletcher and Travers [58], and Mariani [37], and Ascoli [37] have reported cases of quinin idiosyncrasy successfully treated with cinchonin. Moreschi [59] however, has reported a case of quinin hemoglobinuria, in which cinchonin was at first successfully substituted, but after some weeks also caused hemoglobinuria, as did later quinidin and optochin.

**Mode of Action of Cinchona Alkaloids in Malaria.**

The mechanism or chain of events by which a cinchona alkaloid may produce a cure in a case of malaria is unknown. Excellent discussions are given by Yorke and MacFie [43], Lipkin [18], and by Giemsa [60]. It seems certain that the mode of action of cinchona alkaloids is complex and involves some alteration, not only in the viability of the malarial parasite more or less indirectly, but also in the body cells or fluids. As Yorke and MacFie point out, spontaneous recovery from malaria or development of tolerance to the presence of small numbers of parasites, must often occur, or the mass of the native population in the tropics would be exterminated. The factor of resistance to the infection on the part of the patient therefore must be important.

In the case of quinin the active curative agent is probably either quinin itself, or the intermediate aldehyde [18], quininal [10], since the next oxidation product, quitenin, appears inactive [16] [19]. The highest blood quinin concentration likely to be maintained by most massive dosage is probably about 1:60,000 [61]. Kirschbaum [62] found tertian (P. vivax) [2] parasites incubated 5-24 hours with quinin 1:10,000 still
Cinchona Alkaloids and Bark in Malaria

capable of producing malarial infection in six paretics. The action of quinin is therefore probably indirect. Bass [68] found *P. falciparum* succumb in 29 hours to incubation with quinin about 1:3,500, but such a concentration is unlikely to be obtained in the human blood-stream by any means compatible with the survival of the patient.

MILITARY IMPORTANCE OF QUININ.

The restrictions, which it was necessary to apply to quinin distribution during the Great War, show that it would be wise for every power which has a malaria problem, to have under its firm control sources of quinin, including plantations in its sphere of influence, quinin works and adequately trained cinchona chemists, as measures of military protection. Since this is clearly impossible for many powers deeply concerned, it is to be hoped that friendly adjustments may be made possible, in mercy to mankind.

CONCLUSIONS.

Malaria appears to be curable by the administration of any one of quite a large number of cinchona alkaloids. None of these has been definitely proved superior to quinin. Only quinin, quinidin, cinchonin and cinchonidin are sufficiently cheap to be worthy of practical consideration in connection with the treatment of malaria.

Complete comparisons of the value of each of these four alkaloids in all three types of malaria have not yet been made. Quinin cures all types. In benign tertian malaria all four are possibly of equal value. Quinin appears extremely effective in malignant tertian (subtertian) malaria. Quinidin is more effective in malignant tertian malaria than is cinchonin. Quinin and quinidin are probably of equal value in quartan malaria.

There is no clear evidence that quinidin, cinchonidin or cinchonin is more toxic to man than is quinin. Therefore the dosage of quinidin, cinchonidin or cinchonin in malaria would be the same as of quinin, *e.g.* 10 grains (0·65 gram) of the sulphate twice or three times a day initially, for the average adult.

Quinidin or cinchonin may sometimes be successfully used to replace quinin in malaria where quinin idiosyncrasy hinders or prevents administration of quinin. Of these two substitutes quinidin would probably be preferable in malignant tertian fever.

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W. T. Dawson

Cinchona Alkaloids and Bark in Malaria


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