Treatment of Angina Pectoris with Cinchona Alkaloids

By Joseph E. F. RiseMAN, M.D., Lester A. Steinberg, M.D., and George E. AltMAN, M.D.

Reports indicating the value of quinidine sulfate in angina pectoris led to (1) a search for related drugs which were equally effective but less toxic, and (2) a study of the mode of action of these drugs. It was found that quinidine, quinine, cinchonadine, and cinchamidine decrease the frequency of attacks in daily life and increase the exercise tolerance as measured by a standardized test. Quinidine sulfate (0.3 to 0.4 Gm. every eight hours) appears to be the drug of choice from the standpoint of availability and low toxicity as well as effectiveness. The value of these drugs is apparently due to a vasodilating action which in turn is dependent on the presence of the quinoline ring.

Previous studies have demonstrated the value of quinidine sulfate in the treatment of some patients with angina pectoris. However, most general practitioners and, in fact, many cardiologists hesitate to use quinidine in angina because of the complications which occasionally follow its use in the treatment of cardiac arrhythmias. Furthermore, many physicians hesitate to use quinidine in angina pectoris because its mode of action in this condition is not clear. It seemed worthwhile, therefore, to study the activity of drugs related to quinidine in an attempt to find a substance equally effective but possibly less toxic and also to throw some light on the mechanism of action in the treatment of angina pectoris.

The comparative value of 12 pharmaceutical preparations was investigated in patients with angina pectoris. Five of these 12 were cinchona alkaloids (the sulfate salts of quinidine, quinine, cinchonine, cinchonidine, and cinchamidine); these were studied to determine whether drugs which were similar to quinidine in chemical structure but different in cardiodynamic and cardiotoxic effects were of therapeutic value in angina. Procaine amide (Pronestyl) was included because, like quinidine, it is of value in eliminating ectopic ventricular beats. Three synthetic antimalarial preparations (chloroquine, pentaquine and chloroquinidine) were chosen to see whether the therapeutic action in angina might be related to the mechanism responsible for antimalarial activity. Nitroglycerin was used to determine which patients were likely to be benefited by vasodilator drugs and also to compare the effectiveness of the cinchona alkaloids with that of nitroglycerin which is the most effective of the drugs for angina. Penterythritol tetranitrate (Peritrate) was included to compare the frequency and degree of response of the cinchona alkaloids with that of a preparation currently advocated for the treatment of angina pectoris. Finally, placebos were used for control studies and to equalize the beneficial psychologic effects of treatment.

Evaluation of the efficacy of treatment in angina pectoris is difficult. Some of the many factors and problems involved in evaluating treatment in angina will be summarized elsewhere. The methods employed in the present study are based on over 20 years' experience in the Angina Clinic of the Beth Israel Hospital of Boston. In general, these studies are carried out in a group of patients with angina carefully selected for cooperation and a stable clinical course. The methods include clinical evaluation (using what has been called the "double blind test") and, especially, an exercise tolerance test which measures the amount of work which can be done under standardized conditions (in the cold) before angina is in-
The five cinchona alkaloids used in this study were prepared in Holland* in the form of 0.12 Gm. (2 grain) scored, compressed, white tablets, identical with each other in appearance. The dosage used in most instances was 0.360 Gm. (6 grains) or three tablets given three times daily; on arising, at 2.00 p.m., and on retiring. This interval was selected because it has been shown that eight hours after the administration of quinidine sulfate, the concentration in the blood19 and the effect on the heart23 are approximately one-half as great as the maximum. Thus, with 0.4 Gm. (6 grains) every eight hours the effective level in the blood is constantly as high as or higher than the maximum obtained with 0.12 Gm. (3 grains) given at four-hour intervals. Several patients who benefited from the 0.4 Gm. dosage were subsequently given smaller amounts in order to determine the minimum effective dose; patients who failed to respond to 0.4 Gm. were not given smaller doses. In order to check the results obtained with these tablets, quinidine sulfate, packaged by American Pharmaceutical houses in the form of 0.2 Gm. or 0.3 Gm. compressed tablets, and quinine sulfate in the familiar 0.3 Gm. chocolate coated tablets or 0.3 Gm. capsules were also used.

Nitroglycerin. The prophylactic value of nitroglycerin was determined two minutes after a 0.0003 Gm. (1/200 grain) hypodermic tablet had dissolved under the tongue. This, according to previous studies, is the time when the maximum effect of sublingual nitroglycerin is evident.

Procaine amide hydrochloride was used in the form of yellow capsules containing 0.25 Gm. of Pronestyl.† The dosage employed was three capsules (0.75 Gm.) three times a day (at approximately eight-hour intervals).

Synthetic Antimalarial Preparations. Chloroquine‡ was obtained in the form of white compressed tablets of Aralen Diphosphate containing 0.25 Gm. each, and equivalent to 0.15 Gm. of chloroquine base. The dosage used was one tablet three times daily at approximately eight-hours intervals.

Pentaquine§ was used in the form of small, red, sugar coated tablets each containing 13.3 mg. of pentaquine phosphate equivalent to 10 mg. of pentaquine. The dosage was one tablet, three times daily, taken either alone or in some cases together with quinine sulfate, 0.12 Gm., (a dose of quinine usually too small to be of therapeutic effect in angina).

Chlorguanide was obtained as the hydrochloride||

* These five alkaloids were furnished by the Cinchona Institute.
† Pronestyl was supplied by E. R. Squibb & Son.
‡ Aralen Diphosphate was supplied by Winthrop-Sears Inc.
§ Pentaquine was supplied by The Abbott Laboratories.
|| Chlorguanide was supplied by Sharpe and Dohme.
in the form of small white, compressed tablets of 0.1 Gm. each. These, also, were given three times daily.

*Pentaerythritol tetranitrate was used in two forms; white tablets containing 10 or 20 mg. prepared for clinical investigation before the drug was placed on the market,* and also green tablets containing 10 mg. of peritrate.*† The drug was given in doses of 50 mg. four times daily (with meals and before retiring).

Several Patients also received smaller doses.

*Placebos of four varieties were used. Tablets of lactose, flavored with aloin (for bitterness) were prepared to resemble the cinchona alkaloids.‡ Sodium bicarbonate tablets simulated chlorguanide. Yellow capsules identical with Pronestyl and white tablets identical with pentaerythritol tetranitrate were supplied by the manufacturers. No attempt was made to duplicate, with placebos, the distinguishing markings on the Aralen, the red peritrate or the green Peritrate tablets. The 15 forms in which the 12 types of medication were dispensed effectively prevented the patient from differentiating between noneffective and supposedly effective drugs through their physical appearance.

Subjects

The 32 subjects used in this study were selected from at least five times that number who were referred from the Medical and Cardiac Out-Patient Clinics of the Beth Israel Hospital, of Boston. The criteria for selection are discussed elsewhere.⁷ All had angina pectoris, presumably due to arteriosclerosis of the coronary arteries; the distribution according to sex, age, symptoms and findings (table 1) shows them to be a typical group of such patients. Only four patients had neither hypertension, abnormal electrocardiograms, nor cardiac enlargement. All were ambulatory; 13, including 2 women, were gainfully employed in industry; of the remaining 19, the 8 women were able to do at least part of their housework; the 11 men were unemployed due to either their age or their illness.

Methods

All patients visited a special angina research clinic of the Beth Israel Hospital, regularly, at weekly intervals, except for occasional periods due to illness, vacations, or similar causes. The diagnosis, clinical history, frequency of attacks, precipitating factors, duration of periods of spontaneous freedom from attacks, and previous therapy were all re-evaluated both independently and collectively by three investigators. Twelve-lead electrocardiograms were repeated once a year and also whenever a change in clinical course suggested a change or progression of the underlying pathology.

At each visit, the same observer interviewed each patient and ascertained: (1) the patient's evaluation of the effectiveness of the previously administered drug; (2) the actual number of attacks experienced during the previous week; (3) any changes in the patient's daily routine which might have influenced the frequency of attacks; (4) any untoward effects of medication. After the above interview, the exercise tolerance was measured under the standardized conditions used in previous studies² 4, 7, 14, 26 by one or both of the other observers, who, however, did not know what drug the patient was taking. All tests (except those following nitroglycerin) were carried out between one and two hours after the last medication, at least one hour after a light breakfast and following at least 20 minutes rest after coming to the clinic. All tests were carried out in a

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* These experimental tablets were supplied by the Maltbie Laboratories, Inc.
† Peritrate was supplied by the Chilcott Laboratories.
‡ Supplied by Brewer & Company.
special cold room maintained at a temperature of 45 to 55°F. The exercise consisted of repeatedly ascending and descending a two-step staircase (each 9 inches high) until a typical attack of angina was induced or until the patient became fatigued or dyspneic or until the patient had done at least 50 per cent more work than was possible without medication. Only one test was performed on any one day. No test was performed if the patient had experienced an attack within one hour prior to the exercise (table 2).

After the first visit, each patient was given a placebo to be taken three times daily. Observation for several weeks to months established the usual frequency of attacks in daily life and, with some degree of accuracy, the standardized exercise tolerance following placebos. The evaluation of medication was then begun. Further checks of the patients’ exercise tolerance while taking placebos was redetermined frequently during the course of the study.

At each visit, after the exercise tolerance had been measured, the patient returned to the original observer who supplied sufficient medication for the following week. In each instance it was stated or implied that the medication dispensed had been reported as effective in some cases with angina. No definite or constant order of rotation of the drugs was followed except that placebos were invariably given for several weeks before administering any potentially effective medication. If the studies failed to indicate any appreciable benefit, a different medication was prescribed. If the drug was followed by evidence of improvement (i.e., an increase in exercise tolerance of at least 20 per cent as compared with the maximum performed while taking placebos or when taking no medication), a placebo resembling the effective drug was again administered, often (especially with quinine and quinidine) with a different appearance.

**Electrocardiographic Studies**

After the therapeutic value of the drugs had been determined as above, electrocardiographic studies were carried out in some patients who showed a beneficial result in order to determine if the effect was accompanied by objective evidence of a decrease in myocardial anoxia.18, 25

In order to obtain tracings with a minimum of somatic tremor or wandering of the base line during and immediately after exercise, the arm electrodes were applied just below the insertion of the deltoids; the leg electrodes were applied over the bony prominence of the iliac crests; a precordial electrode (measuring 2½ by 1½ inches) was applied in the fifth left intercostal space at the midclavicular line, and the cable was held in the patient’s right hand against his body. A direct recording Sanborn Electrocardiograph was used. Lead 4R only, was recorded.

Evidence of myocardial anoxia is most frequently and most strikingly shown by this lead because anoxia is associated with RS-T depression in V4 and RS-T elevation in V5 while lead 4R is V4 minus V5. Only one lead was recorded on any one day because comparison of tracings before and after medication requires comparison of complexes observed at identical times after exercise.

A 15-second control tracing was taken with the patient standing at rest in the cold room. The exercise was then carried out in the usual manner, but with the electrodes and cable in place and the machine, but not the recording stylus, running constantly. The tracing was recorded immediately before the expected cessation of exercise and for 15 seconds thereafter; the end of exercise was marked. Additional 15 second strips were obtained, one, three, and five minutes after the cessation of exertion. In examining the tracings, the characteristics of 10 consecutive complexes without wandering of the base line were measured and the average obtained.

Before medication (while taking placebos), exercise was continued until a typical attack was induced. After medication, exercise was stopped when the patient had performed the same number of trips as had induced angina while taking placebos.

**Evaluation of Results**

Three methods of evaluation were used and their results were correlated with each other. These three methods were: (1) The exercise tolerance; that is, the amount of work which could be performed (under the standardized conditions described above) before angina was precipitated. (2) The patient’s evaluation of the efficacy of treatment. (3) The number of attacks experienced in daily life during each week of therapy. The results following medication were divided into four categories as follows:

**Marked Response.** This indicates that compared with the maximum amount of work which could be performed while taking placebos, the exercise tolerance in the laboratory was increased either by at least 50 per cent before the patient was forced to stop because of pain or by at least 25 per cent without inducing angina, the exercise being stopped because of dyspnea or fatigue. These results were accepted as indicating a marked response only if they could be obtained repeatedly. Such patients showed, clinically, either complete disappearance or a marked decrease in the frequency of attacks in daily life during the period of medication.

**Moderate Response.** The exercise tolerance in the laboratory was increased by 20 per cent to 49 per cent before the patient developed angina, or the patient was able to do up to 25 per cent more work.

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Table 2.—The Response to Medication in 32 Patients with Angina Pectoris. The Increase in the Amount of Work Which Could Be Performed under Standardized Conditions before an Attack Was Induced

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Placebo, S.E.T.T. Trips</th>
<th>Miscellaneous Medication</th>
<th>Cinchona Alkaloids</th>
<th>Synthetic Antimalarials</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Nitroglycerin</td>
<td>Quinidine</td>
<td>Quinine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Penta-erythritol</td>
<td>Pro-</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tetranitrate</td>
<td>caine</td>
<td>Amide</td>
</tr>
<tr>
<td>H St</td>
<td>M</td>
<td>12-16</td>
<td>210</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>S R</td>
<td>M</td>
<td>36-40</td>
<td>170</td>
<td>42</td>
<td>×</td>
</tr>
<tr>
<td>R S</td>
<td>M</td>
<td>17-20</td>
<td>120+</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>M L</td>
<td>M</td>
<td>32-35</td>
<td>114</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>H N</td>
<td>M</td>
<td>24-29</td>
<td>93+  28</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>R E</td>
<td>M</td>
<td>24-30</td>
<td>93+  20 −3</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>F B</td>
<td>F</td>
<td>12-16</td>
<td>88+  50</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td>H Schl</td>
<td>M</td>
<td>34-40</td>
<td>87+</td>
<td>60+</td>
<td>×</td>
</tr>
<tr>
<td>B K</td>
<td>F</td>
<td>18-20</td>
<td>60</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>L W</td>
<td>M</td>
<td>36-40</td>
<td>55</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>G H</td>
<td>M</td>
<td>25-33</td>
<td>52+  39</td>
<td>67+  R 82+</td>
<td>61  67+</td>
</tr>
<tr>
<td>M B</td>
<td>M</td>
<td>29-33</td>
<td>52+  −9 −12</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>E R</td>
<td>F</td>
<td>20-27</td>
<td>48+  −11 −7</td>
<td>−11  103+    R 4  41</td>
<td>4</td>
</tr>
<tr>
<td>A T</td>
<td>F</td>
<td>18-27</td>
<td>48+  −15 −26</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>A G</td>
<td>M</td>
<td>46-51</td>
<td>39+  0</td>
<td>−2</td>
<td>−29</td>
</tr>
<tr>
<td>P S</td>
<td>M</td>
<td>23-28</td>
<td>32+  −43 −7</td>
<td>25+  R 43+    R 29+  11</td>
<td>−25</td>
</tr>
</tbody>
</table>

**Group 1 Patients**

**Group 2 Patients**

**Group 3 Patients**

* Standardized exercise tolerance test.
+ No attack was induced.
+R Following medication, attacks disappeared in daily life and could not be induced in the laboratory. This condition persisted for at least one month after medication was stopped.
− A decrease in standardized exercise tolerance.
× Medication discontinued because of untoward effect.
TABLE 3.—The Degree of Response to Medication in 32 Patients with Angina Pectoris

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Patients Studied</th>
<th>Therapeutic Response of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>32</td>
<td>16</td>
</tr>
<tr>
<td>Pentaerythritol</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Tetranitrate Amide</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Cinchona Alkaloids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quinidine</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>25**</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Cinchonidine</td>
<td>16*</td>
<td>6</td>
</tr>
<tr>
<td>Cinchamidine</td>
<td>18</td>
<td>2</td>
</tr>
<tr>
<td>Cinchonine</td>
<td>19*</td>
<td>0</td>
</tr>
<tr>
<td>Synthetic Antimalariais</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorellaquine</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Pentaquino</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Chloroguanide</td>
<td>8</td>
<td>0</td>
</tr>
</tbody>
</table>

* One patient and ** three patients respectively discontinued medication because of untoward effects. This result is considered as No Response.

than was possible while taking placebos, the exercise being stopped not by pain but by dyspnea or fatigue. These results were accepted only if they could be repeated. Such patients usually reported a decrease in the frequency of attacks in daily life. Slight Response. These patients were able to do from 10 per cent to 19 per cent more work in the laboratory before developing angina. This degree of response was of no demonstrable clinical significance.

No Response. This indicates less than a 10 per cent increase in exercise tolerance.

RESULTS

In accordance with our previous experience the results of the standardized exercise tolerance test proved to be the most valuable method of measuring the response to therapy. There was a close correlation between an increase in the standardized exercise tolerance test in the laboratory and the response in daily life, in that marked or moderate improvement in exercise tolerance was always associated with a decrease or disappearance of attacks in daily life. On the other hand, most patients felt that they were helped by treatment irrespective of the medication used, and a decrease or disappearance of attacks in daily life was not always accompanied by an increase in exercise tolerance. Thus apparent clinical improvement occurred much more frequently than did objective evidence of real improvement. This is in accord with other studies in the literature which indicate that patients are unable to differentiate between the response to active therapy and the response to placebos. According to the patients’ evaluation of the efficacy of treatment, 23 (of the 32) believed that they were helped by each of the many drugs prescribed, including placebos. There were five patients who believed that some, but not all, medication was helpful; the weeks of poor response, however, were often related to noncardiac symptoms or emotional experiences and could not be correlated with either the medication or the actual number of attacks experienced. The remaining four patients believed that they were not helped by any medication; two of these four actually failed to respond to any therapy.

Similarly, there was no constant correlation between the actual number of attacks experienced during a given week of treatment and either the patient’s estimation of the response to treatment or the exercise tolerance. The clinical course of angina is rarely uniform, and patients who have several attacks weekly frequently experience a week or two of complete freedom from attacks irrespective of treatment. At the onset of the study, when a written record of the frequency of attacks was instituted, most patients reported fewer episodes per week than had been estimated previously. Since this decrease came while taking placebos, the apparent improvement was due not to specific therapy but rather to psychologic factors and more careful observation. Subsequently patients frequently reported further improvement without, however, any change in the actual frequency of attacks.

In general, clinical improvement occurred frequently without objective evidence of improvement and repetition of the same therapy frequently gave different clinical results. An increase in exercise tolerance of more than 20 per cent, however, was practically always accompanied by clinical improvement and such results could be duplicated when the therapy
was repeated even if the appearance of the medication was different.

The usual number of trips which could be performed under standardized conditions by each patient while taking placebos and the change following medication are shown in table 2. The change in ability to work following medication is expressed as the percentage increase (or decrease) in exercise tolerance as compared with the maximum number of trips which could be performed while taking placebos. The frequency with which medication was followed by a decrease in exercise tolerance indicated that this base line is on the high side of his usual exercise tolerance and does not indicate that the patient was made worse by the medication.

Miscellaneous Control Studies

Placebos. Each of the 32 patients received many courses of at least three different placebos during the investigation. The usual range of exercise tolerance was relatively constant. A variation of 2 to 4 trips was observed in 18 patients, from 5 to 6 trips in eight patients and from 7 to 9 trips in the remaining six patients. Thus, the variation from the average standardized exercise tolerance was plus or minus 2 to 9 per cent in 15 patients, plus or minus 11 to 14 per cent in 13 patients and plus or minus 16 to 22 per cent in the remaining four patients.

Nitroglycerin. Between 20 and 30 seconds were required for the 0.0003 Gm. hypodermic tablets of nitroglycerin used in this study to dissolve under the patients’ tongue. When the standardized exercise tolerance was measured two minutes later, 23 of the 32 were able to do an appreciably greater amount of work than was possible when they were taking placebos alone. The prophylactic use of nitroglycerin made it possible to divide patients into three groups as described previously: \(^1\); \(^2\); \(^8\): Group 1 (16 patients or 50 per cent) included those who, following the sublingual administration of nitroglycerin, were able to exercise either to the point of fatigue without experiencing angina or who could do at least 50 per cent more work (under the standardized conditions of the test) than was possible without nitroglycerin. Group 2 (seven patients or 22 per cent) included those who were able to do 20 per cent to 49 per cent more work than was possible without this drug but who, nevertheless, developed a typical attack of angina pectoris. Group 3 (nine patients or 28 per cent) could do no more work (or less than 20 per cent more work) after the sublingual administration of nitroglycerin than was possible without the drug. The patients’ response to nitroglycerin was an index of the likelihood of his response to other effective medication; the results, therefore, are examined accordingly (tables 3 and 5).

Pentaerythritol Tetranitrate. Fourteen patients received 50 mg. of this preparation, four times daily; only three showed objective evidence of a favorable response. All three patients were group 1 subjects; the degree of response was moderate in degree (an increase in exercise tolerance of 20, 28, and 39 per cent, respectively).

Procaine Amide Hydrochloride. Seventeen patients received 750 mg. of this drug, three times daily. Only one showed a beneficial response. Subsequent observation in this patient suggests that this apparent response was due, not to the medication, but rather to a spontaneous partial remission, for her exercise tolerance, even after several months of placebos, had not returned to its original range.

Two of the 17 patients who received procaine amide showed ventricular extrasystoles during their attacks of angina pectoris. The lack of improvement of the angina in these two patients following procaine amide is in contrast to the favorable response reported by Davis in one patient.\(^6\)

The Cinchona Alkaloids

Quinidine, quinine, cinchonidine, and cinchamidine were of considerable value in angina pectoris while cinchonine was of only slight value. In several patients an attempt was made to determine the minimum effective dose. Doses of 0.12 Gm. given at the same time intervals proved of little value. Doses of 0.25 Gm. were usually (but not always) as effective as was 0.3 Gm. or 0.4 Gm.

Quinidine sulfate was administered to 31
Table 4.—The Efficacy of Medication in 25 Patients Who Were Likely to Respond and Also in Nine Patients Who Were Not Likely to Respond

<table>
<thead>
<tr>
<th>Medication</th>
<th>Total Patients Studied</th>
<th>Groups 1 and 2</th>
<th>Group 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of Pts.</td>
<td>Marked or Moderate Response %</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>32</td>
<td>23</td>
<td>100</td>
</tr>
<tr>
<td>Pentaerythritol Tetrani-trate</td>
<td>15</td>
<td>12</td>
<td>25</td>
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<tr>
<td>Procaaine Amide</td>
<td>17</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Cinchona Alkaloids</td>
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<td></td>
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<tr>
<td>Quinine</td>
<td>31</td>
<td>22</td>
<td>73</td>
</tr>
<tr>
<td>Cinchonidine</td>
<td>26***</td>
<td>21**</td>
<td>47</td>
</tr>
<tr>
<td>Cinchamidine</td>
<td>16*</td>
<td>11*</td>
<td>55</td>
</tr>
<tr>
<td>Cinchonine</td>
<td>18</td>
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<td>Synthetic Antimalarials</td>
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<td>Chloroquine</td>
<td>12</td>
<td>10</td>
<td>50</td>
</tr>
<tr>
<td>Pentaquine</td>
<td>11</td>
<td>9</td>
<td>44</td>
</tr>
<tr>
<td>Chloroguanide</td>
<td>8</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

* One additional patient discontinued medication because of untoward effects.
** Two additional patients discontinued medication because of untoward effects.
*** Three additional patients discontinued medication because of untoward effects.

patients. A significant increase in exercise tolerance was shown by 18 of the 31 (58 per cent); these patients included 16 of the 22 subjects in groups 1 and 2 (73 per cent).

In many instances, the increase in exercise tolerance induced by quinidine persisted for two to three weeks after the drug was withdrawn. This is in contrast with our experience with other drugs such as the purines\(^2\) where any improvement usually disappears within one week. Two patients had a complete remission of symptoms: that is, following quinidine therapy they experienced no attacks in daily life, and they were able to exercise until fatigued without developing angina under the usual standardized conditions. In these patients, this remission persisted for at least two months after placebos were substituted for quinidine. In both instances, readministration of quinidine at a later date was again followed by a complete but temporary remission.

Quinine sulfate was given to 29 patients, 3 of whom discontinued the medication. Of the remaining 26, a moderate or marked response was shown by 10 (38 per cent); these 10 were all patients of groups 1 and 2 and constituted 47 per cent of the 21 patients in these two groups. Two patients experienced a temporary remission of angina following quinine.

The comparative value of quinine and quinidine is best shown by the 25 patients whose response to both drugs was tested (table 5). Of these 25 patients, the results in 15 (60 per cent) were identical; four additional patients (16 per cent) showed a response to both drugs but a better response to one than to the other. The remaining six patients (24 per cent), showed a moderate or marked response to one drug but no appreciable response to the other. Cinchonidine sulfate was administered to 17 patients, one of whom omitted the drug. Of the remaining 16 patients, 7 (44 per cent) showed a moderate or marked response; six of these patients were in group 1 (these six made up 55 per cent of the group 1 and 2 patients who received cinchonidine).

Cinchamidine sulfate was given to 18 patients; nine (50 per cent) had a moderate or marked response. All of these nine were in groups 1 and 2 (64 per cent).

Cinchonine sulfate was given to 20 patients, one of whom discontinued its use. Only four of these patients showed a moderate response; no patient showed a marked response.
Untoward reactions were not common and not severe. They usually disappeared with a decrease in dosage. Three patients discontinued the use of quinine, and one patient discontinued both cinchonidine and cinchamidine because of tinnitus or dizziness. This is discussed further, below.

Synthetic Antimalarial Preparations

Chloroquine was given to 12 patients, 5 (42 per cent) of whom responded to a moderate or marked degree; all five were in groups 1 or 2 (50 per cent).

Pentaquine phosphate was given to 11 patients, 4 (36 per cent) of whom responded; all four were in groups 1 and 2 (44 per cent). Because the combination of quinine and pentaquine has been reported to be especially beneficial in the treatment of malaria,29 six patients were given a combination of quinine, 0.12 Gm., plus pentaquine, 13.3 mg., three times daily; the combination showed no synergistic effect. Because of the toxicity of pentaquine, further studies were discontinued.

Chloroguanide hydrochloride was given to eight patients. Only one showed a moderate increase in exercise tolerance. This probably does not represent a true response in this patient but rather a spontaneous partial remission, for the patient continued to have an in-

Table 5.—Comparison of Results in 25 Patients Who Received Both Quinidine Sulfate and Quinine Sulfate

<table>
<thead>
<tr>
<th>Group 1 Patients</th>
<th>Group 2 Patients</th>
<th>Group 3 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>Increase in S.E.T.T. %</td>
<td>Subject</td>
</tr>
<tr>
<td></td>
<td>Quinidine</td>
<td>Quinine</td>
</tr>
<tr>
<td>H St</td>
<td>112</td>
<td>100</td>
</tr>
<tr>
<td>R S</td>
<td>30</td>
<td>40</td>
</tr>
<tr>
<td>M L</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>H N</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>R E</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>F B</td>
<td>62</td>
<td>13</td>
</tr>
<tr>
<td>B K</td>
<td>25</td>
<td>60</td>
</tr>
<tr>
<td>L W</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>G H</td>
<td>67+ R</td>
<td>82+</td>
</tr>
<tr>
<td>M B</td>
<td>27</td>
<td>12</td>
</tr>
<tr>
<td>E R</td>
<td>-11</td>
<td>103+ R</td>
</tr>
<tr>
<td>A G</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>P S</td>
<td>25+ R</td>
<td>43+ R</td>
</tr>
</tbody>
</table>

S.E.T.T. Standardized exercise tolerance test.
- A decrease in exercise tolerance.
+ No attack induced.
+ R Clinical remission of symptoms.

Table 6.—The Effect of Medication of the Electrocardiographic Changes Induced by Exercise

<table>
<thead>
<tr>
<th>Subject</th>
<th>No. of Trips</th>
<th>mm. depression of RS-T segments (average of 10 consec. complexes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebos</td>
<td>Nitroglycerin</td>
</tr>
<tr>
<td>T. Mc.</td>
<td>32</td>
<td>3.5*</td>
</tr>
<tr>
<td>E. R.</td>
<td>29</td>
<td>3.0*</td>
</tr>
<tr>
<td>P. S.</td>
<td>28</td>
<td>2.0*</td>
</tr>
<tr>
<td>A. T.</td>
<td>26</td>
<td>1.5*</td>
</tr>
<tr>
<td>M. B.</td>
<td>32</td>
<td>0.5*</td>
</tr>
</tbody>
</table>

* Attacks of angina were induced by this amount of work only when these patients were taking placebos.

crested exercise tolerance for six months, and readministration of chloroguanide caused no further increase in ability to exercise.

Electrocardiographic Studies

Electrocardiographic studies were carried out in five patients in groups 1 and 2 while they were taking placebos, nitroglycerin, quinidine, quinine or cinchamidine (table 6, fig. 2). The most striking change in lead 4R was observed immediately (within 15 seconds) after the cessation of exercise and consisted of a depression of the RS-T segments; this is in accord with previous studies.25

In these five patients, nitroglycerin not only
prevented attacks of angina, but also decreased markedly the RS-T depression. The average RS-T depression following exercise was 2.1 mm. while taking placebos and 0.65 mm. after nitroglycerin. In general, those who showed the greatest RS-T changes while taking placebos showed the greatest improvement in the exercise electrocardiogram after nitroglycerin.

The RS-T depressions of the two patients who benefited from quinidine were 3.5 mm. and 1.5 mm., respectively, while taking placebos, as compared with 1.25 mm. and 1.0 mm., respectively, while taking quinidine. Similarly, the three patients who benefited from quinine showed RS-T depressions of 3.0 mm. 2.0 mm. and 1.5 mm. before, and 2.23 mm. 0.75 mm. and 0.75 mm., respectively, after this drug. The results with cinchamidine, although not so striking, also showed a diminution of the anoxic changes in the exercise electrocardiogram; the RS-T depressions measured 3.0 mm. 1.5 mm. and 0.5 mm. following placebos and 2.0 mm. 1.5 mm. and 0.0 mm., respectively, following cinchamidine.

**Comment**

**Evaluation and Significance of Results**

The above studies illustrate the importance of adequate control studies in measuring the value of treatment in angina pectoris, and also the advisability of comparing the effect of the drug under study with the effects of other medication of accepted or potential value. By this means we can clearly demonstrate the contrast between the negative results obtained with three of the preparations (placebos, procaine amide, and chlorguanide), the moderately favorable results with two drugs (cinchonine and pentaerythritol tetranitrate) and the positive results obtained with seven other drugs (nitroglycerin, quinidine, quinine, cinchonidine, cinchamidine, chloroquine and pentaquine); this contrast emphasizes the significance of the results with the latter seven drugs.

These studies also illustrate the value of considering separately the results obtained in patients likely to respond to medication and in those not likely to react favorably. Thus, of the 16 patients who showed a marked response to nitroglycerin, nine showed a marked response and six more showed a moderate response to one or more of the cinchona alkaloids. Similarly, of the seven patients who showed a moderate response to nitroglycerin, six showed a moderate response to other drugs. In contrast, only two of the nine patients who showed no response to nitroglycerin showed a moderate response to other drugs. In our experience, the frequency of group 3 patients has varied from 28 per cent of the subjects in the present study to 40 per cent in previous studies with larger numbers of subjects. Unless the negative results in these nonreacting patients are separated from the results obtained in patients more likely to respond to medication, the beneficial results in the latter group are likely to be overlooked or minimized because of dilution with negative results.
It is advisable to compare the efficacy of the cinchona alkaloids with that of other therapy used in angina. From the results of the above and also from the results of previous studies, nitroglycerin ranks highest in the frequency and the magnitude of its prophylactic effect in angina pectoris; its practical value is limited, however, by its relatively short duration of action.\textsuperscript{2} Pentaerythritol tetranitrate is obviously of some value in some patients, but it is much less effective than other available drugs including some of the cinchona alkaloids. Comparison with previous studies indicates that the effectiveness of the cinchona alkaloids is of the same magnitude as that of nontoxic coated theobromine sodium acetate and aminophylline in appropriate doses\textsuperscript{15} and is considerably greater than that of oral papaverine\textsuperscript{21} or khellin.\textsuperscript{20} The cinchona alkaloids rank, therefore, among the most effective of medicinal agents available for the treatment of angina pectoris.

Mechanism of Action

The pharmacologic action of the cinchona alkaloids is incompletely understood even in the treatment of malaria in which it has been used for centuries. They have been called “general protoplasmic poisons,” presumably because of their varied action on so many different tissues and organisms and especially because of their antiseptic action on many unicellular organisms (bacteria, yeast, infusoria, plasmodia, trypanosomes, spirochetas, amebae and spermatozoa). The use of this term “protoplasmic poison” is unfortunate, for it contributes to the fear of employing these drugs and it minimizes the fact that, like other drugs which may be toxic under some circumstances, they are valuable therapeutic agents when used properly.

It is probable that the cinchona alkaloids are effective in angina pectoris because of a vasodilator action. Thus, they are more effective in patients who respond to nitroglycerin and are least effective in patients who fail to respond to nitroglycerin. Furthermore, when these drugs are effective they also prevent or decrease the electrocardiographic evidence of anoxia induced by exercise. That quinidine and quinine have a vasodilating action is indicated by coronary blood flow studies in laboratory animals.\textsuperscript{31}

It is probable that the cinchona alkaloids owe their effectiveness in angina pectoris to the presence of the quinoline ring (fig. 1). This would explain why chloroquine and pentaquine are also effective while chlorguanide, which has a phenol rather than a quinoline ring, is of no value. In this regard, it is of interest to note that papaverine, ethaverine, and pavril also contain the quinoline ring and are also of value in angina pectoris although the latter three are much less effective in angina pectoris than are the cinchona alkaloids.\textsuperscript{21--23}

The quinoline nucleus, together with many of its derivatives, possesses varied pharmacologic activity inducing antiseptic, anesthetic, and circulatory effects and a depressant action on the nerve endings.\textsuperscript{31--34} Advantage is taken of these properties in therapeutics. The antiseptic properties are employed in preservatives (e.g., chinosol), amebicides (e.g., Vioform) and antimalarials (e.g., quinine). The anesthetic effects are seen with some quinine salts and especially Nupercaine. The circulatory effects have been incompletely studied, but include slowing of the heart, increase in the refractory period and vasodilation which is antagonistic to the action of epinephrine.\textsuperscript{35, 34} The effect on the nerve endings has been suggested as the mode of action of quinine and quinidine in night cramps.\textsuperscript{35--36} The many quinoline derivatives each possess all of these activities in varying degrees although one effect may outbalance the others so as to seem quite specific. Thus quinidine is much more effective in the treatment of arrhythmias than the other cinchona alkaloids, and cinchonine is less effective in angina pectoris. Quinoline itself (as 8-hydroxyquinoline sulfate) has been found to be of slight value in angina pectoris.\textsuperscript{20}

The possible roles of other mechanisms in achieving therapeutic results in angina pectoris deserve comment. Quinidine and also procaine amide have been advocated for the treatment of angina pectoris where exertion induces ventricular premature beats.\textsuperscript{1, 5, 6} It is unlikely that the beneficial results observed in the present series are due to this action, for few
of the patients developed premature beats on exertion or during attacks, and procaine amide was not found of value in the present group. Furthermore, it has been shown that in the treatment of arrhythmias (auricular fibrillation, for example), quinidine is far more effective than are quinine, cinchonidine, or cinchamidine, whereas in angina pectoris these drugs are almost equal in value.

The similarity of the clinical effectiveness of quinine and quinidine in both angina pectoris and in night cramps (which are not infrequent in patients with angina) is of interest. It is presumed that in night cramps the cinchona alkaloids act by blocking the nerve impulses at the myoneural junction. The evidence that this is the sole mode of action is far from conclusive, however, and the possibility of other pharmacologic activity which may be of value in both conditions, deserves further study.

Toxic and Untoward Effects

The potential toxicity, as well as the usual safety of the cinchona alkaloids is well known owing to their widespread use in the treatment of malaria. For convenience, the undesired reactions may be divided into A, the toxic or more serious effects, and B, the untoward or less serious effects.

A. Toxic Effects. These include the reactions which are potentially dangerous to life and necessitate immediate cessation of cinchona therapy. In our experience, with this series and with a large number of patients treated with quinidine since 1937, such reactions are rare in patients with angina pectoris. They include:

1. Hypersensitivity Reactions. Shortly after an initial dose of one of these cinchona alkaloids a patient may show collapse, asthmatic breathing, and other signs due to an inherent or acquired hypersensitivity. Such reactions are, fortunately, very rare; they occur with many other drugs as well. We have not, as yet, observed such reactions in patients with angina pectoris.

2. Toxic Cardiac Effects. The frequency of complications and deaths arising from the use of quinidine in the treatment of cardiac arrhythmias, especially chronic auricular fibrilla-

tion, is well known and is probably the main reason why many physicians hesitate to use this drug. We have never encountered this type of reaction with the use of quinidine in the treatment of large numbers of patients with angina pectoris and normal cardiac rhythm. Auricular fibrillation is relatively uncommon in patients with angina pectoris; quinidine should not be used in such patients. These and other cardiotoxic effects of quinidine will probably be extremely rare with the other cinchona alkaloids including quinine.

3. Miscellaneous Toxic Reactions. After one or more days of therapy, a patient may develop thromboeytopenic purpura or fever or other symptoms indicative of a toxic effect on the hemopoietic or other systems. Here again, this type of reaction is rare. In over 16 years of using quinidine for the treatment of angina pectoris we have encountered one instance of fever in the treatment of a patient not included in the present series. Approximately 10 days after taking 0.6 Gm. of quinidine sulfate three times daily, this 56 year old woman with angina pectoris and ventricular extrasystoles developed malaise, a temperature of 103 F. and a generalized morbilliform rash. This all subsided within 48 hours after the drug was discontinued. In addition to this case there are a total of 14 others reported in the literature.

B. Untoward Effects. These include the reactions which are uncomfortable but rarely dangerous to life. They usually disappear with a decrease in dosage, and they do not necessitate omission of therapy.

1. Diarrhea is the most common untoward reaction to these drugs; it is rarely troublesome and disappears quickly with a decrease in dosage to 2 or 3 grains three times daily. Many patients welcome this looseness of the bowel movements as a change from a habitually more constipated state; in fact, several patients have asked, “Please give me that good physic that you gave me last week.” It is probably best to avoid its occurrence, for it may prevent adequate absorption of the drug.

2. Nausea may be very troublesome in an occasional patient. It usually disappears, however, with a decrease in dosage. Antacids may help.
3. **Tinnitus** is mentioned in all textbooks of pharmacology. It is not common in our experience even when patients received 1.1 Gm. daily for weeks or months. Two patients in the present series, however, discontinued quinine because of ringing in the ears.

4. **Dizziness** was complained of by one patient who had adverse comments to make about all therapy including placebos. Because of dizziness he discontinued the use of both cinchonidine and cinchamidine.

5. **Urticaria** was the most troublesome of the untoward effects, but here again it may disappear with a decrease in dosage. It caused two patients to discontinue quinine. It did not appear until the drug had been administered for the second time; this suggests that the reaction may be due to an acquired sensitivity.

**Summary and Conclusions**

1. The efficacy of 12 preparations in the treatment of angina pectoris was studied in 32 subjects with such symptoms.

   The preparations included placebos, nitroglycerin, five cinchona alkaloids (quinidine, quinine, cinchonidine, cinchonine, and cinchamidine), procaine amide, chloroquine, pentaquine, chlorguanide, and pentaerythritol tetranitrate.

   The methods of evaluation included: (a) a comparison of the clinical response with measurements of the exercise tolerance under standard cold conditions, and studies of the effect of medication on the electrocardiographic changes induced by exercise; (b) comparison of the value of the cinchona alkaloids with the ineffective placebos, the very effective nitroglycerin and the slightly effective pentaerythritol tetranitrate, and (c) analysis of the results in two separate groups of subjects, that is, those likely to respond to vasodilator therapy and those not likely to respond to such therapy.

2. Four of the cinchona alkaloids (quinidine, quinine, cinchonidine, and cinchamidine) proved to be highly effective in some but not all patients with angina. The patients most likely to respond to these cinchona alkaloids were those who responded well to nitroglycerin. No toxic and few untoward effects were observed.

Quinidine and quinine are among the most effective of the drugs now available for the treatment of angina pectoris.

3. Quinine is the drug of choice because of low toxicity, effectiveness, and low cost to the patient. Quinidine possesses little of the potential cardiotoxic effects of quinidine. The latter drug is equally available but somewhat higher in cost. Quinidine is possibly somewhat more effective in angina than is quinine.

4. The effectiveness of the cinchona alkaloids in angina pectoris is due, at least in part, to a vasodilator action. The quinoline ring is probably the portion of the molecule primarily responsible for the therapeutic effect.

**Sumario Español**

1. La eficacia de 12 preparados en tratamiento de angina de pecho fue estudiada en 32 sujetos con tales síntomas.

   Los preparados incluyeron placebos, nitroglicerina, cinco alcaloides de cinchona (quinidina,quina, cinchonidina, cinchonina y cinchamidina), amida de procaína, cloroquina, pentaquina, cloroguanida y el pentaeritrol tetranitrito.

   Los métodos de evaluación incluyeron: (a) una comparación en la respuesta clínica con medidas de tolerancia al ejercicio bajo condiciones uniformes de frío y estudios de efecto de el preparado en los cambios electrocardiográficos inducidos por el ejercicio; (b) comparación del valor de los alcaloides de cinchona con los placebos inefectivos, la muy efectiva nitroglicerina y el muy ligeramente efectivo pentaeritrol tetranitrito y (c) análisis de los resultados en dos grupos separados de sujetos, esto es, aquellos que probablemente responderían a la terapia vasodilatadora y aquellos que probablemente no responderían a tal terapia.

2. Cuatro de los alcaloides de cinchona (quinidina, quina, cinchonidina y cinchamidina) probaron ser altamente efectivos en algunos pero no en todos los pacientes con angina. Los pacientes que con mayor probabilidad respondían a los alcaloides de cinchona fueron aquellos que respondieron bien a la nitroglicerina. Ningún efecto tóxico y pocos no deseados fueron observados.
La quinidina y la quinina están entre las drogas más efectivas disponibles para el tratamiento de la angina de pecho.

3. La quinina es la droga preferida por su baja toxicidad, efectividad y bajo costo para el paciente. La quinidina posee poco de los efectos potenciales cardiotóxicos de la quinidina. La última droga es igualmente disponible pero algo más alta en costo. La quinidina es probablemente algo más efectiva en la angina que la quinina.

4. La efectividad de los alcaloides de cinchona en la angina de pecho se debe, por lo menos en parte, a acción vasodilatadora. El anillo de quinolina es probablemente la porción de la molécula primariamente responsable por su efecto terapéutico.

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30 Unpublished data.
Treatment of Angina Pectoris with Cinchona Alkaloids
JOSEPH E. F. RISEMAN, LESTER A. STEINBERG and GEORGE E. ALTMAN

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