growth, on the whole, was good. In fact, more than 60 per cent of them grew somewhat more rapidly than according to the average weight chart. Osteoporosis and other conditions of the bone were thought of and studies were made of these individuals to see whether any evidence could be gained of bone deficiency or of calcium deposit deficiency, other than rickets. We were not able to make them out. This study was begun four years ago. At that time, to my knowledge, serial roentgen studies of the wrist were not known, and we did not use them in this series. The same might be said with regard to the dose of viosterol. It was a new product, and the dose of 10 minims (0.6 cc.) which was advised in those days is now somewhat increased by some authorities. But there was in those days some fear expressed that overdoses could be used. For that reason, since we had started with the single roentgen examination and with the initial dose, 10 minims, we did not change with the appearance of these newer ideas with regard either to diagnosis or to the preventive treatment of the condition. The radiation used in these series did average at least eleven minutes a month. That one may find rickets and another one might not find rickets in groups of babies is entirely possible. We made a positive diagnosis on every baby which had at least two, even though very mildly developed, symptoms, ordinarily called rachitic changes. I speak of the clinical diagnosis. We had to do that in order to get enough positive rickets in the series to make comparison between the usefulness of the two antirachitic agents. I am indeed delighted to have my knowledge increased with regard to the use of salmon oil. I had not until now known that salmon oil was even active as an antirachitic agent. Cod liver oil concentrates or cod liver oil tablets were not used in this series at all.

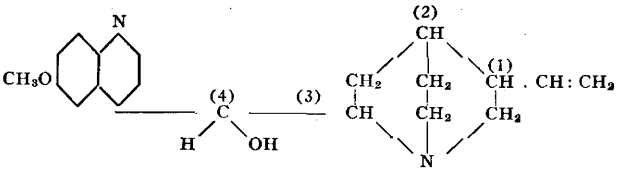
EFFICACY OF QUINIDINE IN MALARIA

J. P. SANDERS, M.D.
CASPIANA, LA.
AND
W. T. DAWSON, M.A.
GALVESTON, TEXAS

Quinidine is worth consideration in connection with the treatment of malaria. In some recorded cases of urticarial,[1] asthmatic or anaphylactoid,[2] or coryzal [3] reaction to quinine, quinidine has been found to produce no such annoying side effect. While such patients are not numerous, every one of them presents a troublesome problem, and it is in the hope that quinidine may be found useful in some such cases that we call attention to this drug, a natural alkaloid of cinchona, the antimalarial value of which has been widely attested.

Quinidine, an optical isomer of quinine, was discovered in 1833 by Henry and Delondre. In 1834, "deceived by the analogies between quinidine and quinine," they decided that quinidine was merely a "hydrate of quinine." [4] In 1847, Winckler discovered the alkaloid now known as cinchonidine and applied to it the name quinidine, which was free; thus began a confusion of these two alkaloids with each other that echoes still. The relation between quinine and quinidine was first definitely shown in 1853 by Pasteur, who 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." [4] Pasteur proposed the new name cinchonidine for Winckler's quinidine, and reappropriated the name quinidine for the quinidine of Henry and Delondre. Pasteur's terminology is now in use.

Chemical research has shown the presence in the quinidine formula of four asymmetrical carbon atoms. These are all dextrorotatory in effect in quinidine, but



Formula of quinidine and quinine. The asymmetric carbon atoms are numbered.

in quinine probably both the third and fourth (see formula) are levorotatory in effect,[5] and there is a net levorotatory balance.

The source of quinidine is cinchona bark, in most varieties of which it is the least abundant of the crystallizable alkaloids commercially separated. In 1929, the bark extracted by a large quinine works averaged 4.935 per cent quinine and only 0.14 per cent quinidine.[6] A variety of Cinchona ledgeriana exists, however, called Chinidinifera,[7] in which the quinidine content may be very high, showing quinine 1.86 per cent and quinidine 3.86 per cent in recent analysis; [7] this variety is not widely known and has probably not been much cultivated. The chief impurity likely to be present in quinidine is hydroquinidine (from 6 to 30 per cent),[8] which has been shown by Giemsa and Werner [1] to possess high antimalarial activity; this has been confirmed by Bevil.[9] Rabe [5c] has succeeded in preparing quinidine by suitable chemical treatment of quinine.

The lethality of quinidine for mammals is probably greater than that of quinine, as judged from observations on the cat,[10] rat [11] and guinea-pig.[12] The subcutaneous dose of quinidine in terms of anhydrous alkaloid killing 50 per cent of a group of thirty small male guinea-pigs is about 130 mg. per kilogram against about 200 for quinine. Hydroquinidine is possibly slightly less toxic than quinidine.[12] All three alkaloids in doses nearly or quite lethal are likely to cause clonic convulsions in the guinea-pig, and probably in man, judging from the observations of Lavier on five cases (three

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1. Giemsa, G., and Werner, H.: Erfahrungen mit weiteren dem Chinin nahestehenden Alkaloiden, und einigen ihrer Derivate bei Malaria (Chinidin, Hydrochinidin, Cinchonin, Hydrocinchonin, Cuprein, Chinäthylin, und Chinopropylin), Arch. f. Schiffs- u. Tropen-Hyg. **18:** 12, 1914.

2. (*a*) Dawson, W. T., and Garbade, F. A.: Idiosyncrasy to Quinine, Cinchonidine and Ethylhydrocupreine and Other Levo-Rotatory Alkaloids of the Cinchona Series: Preliminary Report, J. A. M. A. **94:** 704 (March 8) 1930; J. Pharmacol. & Exper. Therap. **39:** 417 (Aug.) 1930. (*b*) Sanders, J. P.: Treatment of a Patient with Malaria and Acquired Anaphylactoid Reaction to Quinine: Successful Use of Quinidine, J. A. M. A. **97:** 850 (Sept. 19) 1931.

3. Dawson, W. T., and Newman, S. P.: Acquired Allergic Coryzal Reaction to Quinine, but Not to Quinidine or Quitenine, J. A. M. A. **97:** 930 (Sept. 26) 1931.

4. (*a*) Léger, E.: Les alcaloides des quinquinas, Soc. d'éditions scientifiques, Paris, 1896. (*b*) Dawson, W. T.: Cinchona Alkaloids and Bark in Malaria, Internat. Clin. **2:** 121 (June) 1930; (*c*) J. Roy. Army M. Corps **56:** 178 (March) 1931.

5. (*a*) Henry, T. A.: The Plant Alkaloids, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1924. (*b*) King, Harold, and Palmer, A. D.: The Resolution of Tropic Acid and the Stereochemical Configuration of the Cinchona Alkaloids, Tr. Chem. Soc. **121:** 2578, 1922. (*c*) Rabe, Paul: Über die Reduktion der China-Ketone zu China-Alkoholen und über die sterische Umlagerung von China-Alkaloiden, Ann. d. Chem. **492:** 242, 1932.

6. Howard, B. F.: Some Notes on the Cinchona Industry, Chem. News **142:** 129 (Feb. 27) 1931.

7. (*a*) Kerbosch, M.: Personal communication. Dr. Kerbosch is director of Government Cinchona Plantations, Java. (*b*) Dawson, W. T.: Antimalarial Value of Cinchona Alkaloids Other Than Quinine, South. M. J. **25:** 529 (May) 1932.

8. Howard, B. F.: Personal communication. Dawson (footnote 7 *b*).

9. Bevil, H. G.: Personal communication.

10. Weiss, Soma, and Hatcher, R. A.: II. Studies on Quinine, J. Pharmacol. & Exper. Therap. **30:** 327 (Feb.) 1927; III. Studies on Quinidine, ibid. **30:** 335 (Feb.) 1927.

11. Nelson, Erwin E.: Studies on Quinine and Quinidine: IV. A Note on Their Comparative Toxicity, Arch. internat. de pharmacodyn. et de thérapie **33:** 204, 1927.

12. Dawson, W. T., and Harms, H. P.: Previously unpublished observations.

fatal) of poisoning of French soldiers with quinine;[13] the dose was about 16 Gm. of the hydrochloride, in solution, by mouth. No complete physiologic analysis of these convulsions has yet been made. "Useful Drugs" recommends in auricular fibrillation dosage of 5 grains (0.324 Gm.) of quinidine sulphate four times daily. Hornor[14] has given as high as 150 grains (9.7 Gm.) a day in auricular fibrillation, but this appears very high.

Quinidine and quinine appear to be rapidly absorbed from the intestine, partly destroyed in the liver[10] and more or less largely excreted in the urine, depending on the individual, and in 5 grain doses usually give rise to a urinary turbidity with potassiomercuric iodide reagents.

Quinidine has come into prominence of late years in connection with the treatment of auricular fibrillation. Quinidine sulphate, however, has been official in the U. S. Pharmacopeia since 1884, having apparently been included because of its antimalarial efficacy, now largely forgotten.

The earliest large scale therapeutic observations on quinidine were made by the Madras Chinchona Commission in 1866-1868 in southern India.[15] "Mostly at stations and in localities known to be malarious," their representatives used quinidine in 1,040 cases of fevers considered "of the true paroxysmal character caused by malaria" and in 1,025 cases the "febrile paroxysms" ceased, a percentage of clinical cure of 98.5 per cent.

Since the discovery of the malarial parasite, the antimalarial efficacy of quinidine has been confirmed by German,[1] British,[16] French[17] and Italian[18] workers on totals of more than 400 cases of benign tertian and 120 cases of estivo-autumnal fever, and 11 of quartan. Some have classed the drug as inferior to quinine, some as superior, and some as of equal value.

The toxic effects reported from quinidine treatment are strikingly similar to those of quinine. The Madras Commission[15] in a report on 846 patients treated with doses of from 2 to 20 grains (0.13 to 1.3 Gm.) of

13. Lavier, G.: Sur cinq cas dont trois mortels d'intoxication aiguë par la quinine, Bull. Soc. path. exot. **24**: 184, 1931.

14. Hornor, A. A., in discussion on Barrier, C. W.: The Use of Quinidine in the Treatment of Ectopic Rhythms, J. A. M. A. **89**: 745 (Sept. 3) 1927.

15. Reports of the Madras Chinchona Commission Contained in Blue Book "Return. East India (Chinchona Cultivation). 9 August 1870," London, His Majesty's Stationery Office, 1931. Out of print, 1932. Summary by Dawson, footnote 4*b*.

16. (*a*) MacGilchrist, A. C.: The Relative Therapeutic Value in Malaria of the Cinchona Alkaloids—Quinine, Cinchonine, Quinidine, Cinchonidine and Quinoidine, and the Two Derivatives, Hydro-Quinine and Ethyl-Hydro-Cupreine, Indian J. M. Research **3**: 1, 1915-1916. (*b*) Acton, H. W.: Researches on the Treatment of Benign Tertian Fever, Lancet **1**: 1257 (June 12) 1920. (*c*) Medical Research Council, Clinical Comparisons of Quinine and Quinidine, Special Report Series, no. 96, London, His Majesty's Stationery Office, 1925. (*d*) Fletcher, William: Notes on the Treatment of Malaria with the Alkaloids of Cinchona, London, John Bale, Sons & Danielsson, Ltd., 1928. (*e*) Sinton, J. A., and Bird, W.: Studies in Malaria, with Special Reference to Treatment. The Cinchona Alkaloids in the Treatment of Benign Tertian Malaria, Indian J. M. Research **16**: 725 (Jan.) 1929. (*f*) Sinton, J. A.: Summary of Experiments Made in India on the Value of the Different Cinchona Alkaloids in the Treatment of Malaria, Records of the Malaria Survey of India **1**: 429, 1930.

17. Marchoux, E.: Tous les alcaloïdes du quinquina possèdent la même action curative sur le paludisme, Bull. soc. path. exot. **12**: 307, 1919.

18. Ascoli, V.: Alcuni alcaloidi della china nella cura della malaria, Policlinico (sez. prat.) **33**: 370 (March 15) 1926. Lega, G.: Il chineto, la cinconina, la chinidina nella cura della malaria, Riv. di malariol. **7**: 629 (Sept.-Oct.) 1928.

Clinical Results of a Four-Day Course of Treatment of Smear-Diagnosed Malaria *

Patient's No.; Age, if a Child	Effect of Four Day Treatment After Beginning of Treatment: Chills	Days of Fever	Days to Clinical Recovery	Blood Smear	Clinical Relapses	Further Treatment†
White				**A. Quinidine in Benign Tertian Malaria**		
2	0	1	4	—(10) —(370)	0 in 410	None
3	0	1	3	—(39) —(360)	0 in 400	None
4	0	0	3	—(39) —(360)	0 in 400	None
5	0	2	4	—(6) —(330)	Headache at 30	One at 30
6	0	2	5	—(10) +(94) —(300)	One at 94	One at 94
9	0	2	4	—(10) —(285)	0 in 325	None
11	0	1	3	—(5) +(270)	One at 270	One at 270
18	0	1	3	—(5)	0 in 200	None
27	0	1	3	—(90) —(220)	0 in 255	None
43	0	1	3	—(30) +(180)	0 in 220	One at 190
45	0	1	3	—(10) —(180)	0 in 220	None
49	0	1	4	—(190)	One at 30	Quinine at 30
56	0	1	3	—(13) —(152)	0 in 190	None
58	0	1	4	—(10) —(140)	0 in 180	None
Negro						
8	0	2	4	—(11) —(125) —(250)	0 in 290	None
24	0	2	4	—(30)	0 in 180	None
31	1	1	7	—(10) +(45) M.T.‡	0 in 150	One at 50
35	0	3	10	—(50) —(220)	3 in 260	None
39	0	2	10	—(45) —(215)	0 in 215	None
42	0	1	7	—(20)	0 in 90	None
48	1	2	7	—(20) —(150)	0 in 170	None
21	2	1.4	4.7		4	6
				B. Quinidine in Estivo-Autumnal Malaria		
White						
33	0	1	4	—(10)	0 in 40	None
38	0	1	3	—(14)	0 in 40	None
61 (3)	0	1	3	—(10) —(30)	0 in 110	None
62 (16)	0	1	3	—(7) +(14) +(102)	Two	Clinical relapses at 14 and 28; quinidine repeated each time with prompt cessations of symptoms
63 (12)	0	1	3	—(7) +(14) +(102)	Two	
64 (10)	0	1	4	—(10) —(102) +(120)	One at 120	One at 120
Negro						
17	1	8	5	—(95) —(148)	0 in 148	None
20	0	1	2	—(88) —(140)	0 in 140	None
21	0	3	7	—(83) —(135)	0 in 135	None
25	0	1	4	+(64) —(117)	0 in 157	One at 64
26 (6)	0	1	4	+(64) —(117)	0 in 157	One at 64
28	0	1	2	—(64) —(117)	0 in 157	None
37	0	2	10	—(60) +(120)	0 in 150	One at 150
41 (14)	0	3	7	—(30) —(210)	0 in 250	None
50	0	3	14	—(20) —(160)	0 in 195	Took 10 grains of quinine about 60 days
51	0	1	2	—(10) —(150)	0 in 150	None
52	0	3	7	—(15) +(150)	0 in 170	One at 170
54 (4)	1	3	10	—(155)	0 in 155	None
60	0	3	10	—(105)	0 in 105	None
19	2	1.8	5.5		3	8

Clinical Results of a Four-Day Course of Treatment of Smear-Diagnosed Malaria—Continued

Patient's No.; Age, if a Child	Effect of Four Day Treatment After Beginning of Treatment: Chills	Days of Fever	Days to Clinical Recovery	Blood Smear	Clinical Relapses	Further Treatment
C. Quinine in Benign Tertian Malaria						
White						
10	1	4	14	—(45) —(250)	0 in 290	None
29	1	4	14	—(230)	0 in 270	None
Negro						
1	0	7	32	—(7) —(14) —(21) —(360)	3 (7, 14, 21)	Repeated quinine at 7, 14, 21 days; quinidine at 28; clinically well for 370
5	1	2	4	—(120) —(270)	0 in 310	None
6	0	1	4	—(120) —(270)	0 in 310	Chills stopped before treatment started
9	3	7	14	—(7) —(105) —(255)	One at 7	Quinidine at 7; prompt recovery
11	3	3	14	—(14) —(240)	One at 7	Same as case 9
12	0	8	28	—(100) —(136) —(241)	One at 100	Quinidine at 100
17	1	7	14	—(110)	0 in 150	None
18	2	3	7	+(78) —(105)	0 in 105	Quinidine at 85
19 (7)	0	3	4	+(78) —(105)	0 in 105	Quinidine at 85
22	1	5	14	—(10)		
23	1	7	10	—(7) —(30)	One at 7	Quinidine started at 7
25	1	4	5	—(50) +(135)	One at 100	Quinine and chill tonic
26	0	1	3	—(50) +(130)	0 in 135	Quinidine at 135
28	1	4	10	—(30)	0 in 190	None
32	0	3	7	—(35) —(120)	One at 150	Quinidine at 150
33	0	2	14	—(35) —(130)	0 in 130	None
34 (13)	0	2	7	—(30)	0 in 150	None
35	1	3	7	—(30)	0 in 130	None
36	3	7	14	—(137)	0 in 137	None
37	1	3	7	—(135)	0 in 175	None
38 (5)	0	3	7	—(30) —(130)	0 in 170	None
46	0	7	14	—(10) —(130)	One at 5	Quinidine at 5
50	2	3	14	—(10) —(140)	0 in 170	None
53	0	2	7	—(133)	0 in 178	None
57	1	3	7	+(135)	0 in 175	Quinidine at 140
58	0	3	7	—(135)	0 in 175	None
59	0	1	5	—(30)	0 in 95	None
60	0	3	7	—(10)	0 in 195	None
30	16	3.8	10.5		8	12
D. Quinine in Estivo-Autumnal Malaria						
Negro						
8	0	3	14	—(5) +(92) —(300)	0 in 300	Quinine at 100
21	0	3	14	—(68) —(270)	0 in 310	None
27	0	3	14	+(48) —(210)	0 in 210	Quinine at 50
30 (3)	0	7	14	+(48) —(210)	0 in 240	Quinidine at 60
40	0	2	7	—(15) +(180)	0 in 210	Quinidine at 200
42	2	14	28	—(175)	0 in 175	Quinine and chill tonic at 14 (self prescribed)
43	0	7	14	—(175)	0 in 175	None
45	0	1	7	—(134)	0 in 134	None
47	0	2	7	—(169)	0 in 200	None
48	2	3	7	—(132)	0 in 172	None
51	0	2	14	+(165)	0 in 180	Quinidine at 180
55	2	3	10	+(5) —(10) —(90)	1 at 5	Quinidine at 5
61	2	7	21	+(7) —(14) —(90)	1 at 10	Quinidine at 10
13	4	4.4	13.1		2	8

* Daily single doses consisting of 10 grains of quinine sulphate or quinidine sulphate; the course was repeated as needed. The numbers in last three columns refer to days after beginning the treatment.

† "One at 50" or "quinidine at 50" means one four day course of 10 grains daily starting at fifty days from the beginning of the initial treatment.

‡ Malignant tertian (estivo-autumnal).

quinine and 664 treated with quinidine in doses of from 2 to 30 grains (0.13 to 1.95 Gm.) gave as toxic effects of both alkaloids deafness, singing in the ears, purging, vomiting, vertigo, "excitement" or "depression" of the circulation. The differences cited between the two are that the purging after quinidine is called bilious, and that quinine caused a few headaches.

Malariologists in general appear to have considered quinidine a safe drug, but the British Medical Research Council [19] publishes a warning note. Acton, "in a series of somewhat weakly and illnourished Indian patients treated by him for malaria with quinidine, has in several instances observed pronounced depression of the heart's action, which he attributes to the effect of quinidine." Syncope was observed, and two sudden deaths, the latter in patients also suffering, however, from kala-azar. Two things should be here noted. Kala-azar may be rapidly fatal; the dose of quinidine used is not stated. Quinidine sulphate has been given in malaria in 270 cases in doses of 10 grains (0.65 Gm.) twice daily for a week or more without recorded accident.[20]

Hegner, Shaw and Manwell [21] found quinidine and quinine practically equal in bird malaria, but there seems to have been little interest in this country in the clinical aspects of the question. Our own interest in the matter dates from experience of two cases in which quinine caused an asthmatic or anaphylactoid type of reaction while quinidine appeared harmless,[2] despite the assertion of various cardiologists that quinidine should not be given to subjects with quinine idiosyncrasy.

In 1930, one of us (J. P. S.) used quinidine in 39 cases of malaria with good results.[22] Then we decided to try to compare it with quinine, the antimalarial value of which is well established. With this in mind in 1931, we decided to treat alternate patients with quinine and quinidine. The same dosage of sulphate was used for the same length of time and in the same manner. This was carried out except in two or three patients who had taken quinidine the year previously and refused to take quinine. The method of giving 10 grains daily three hours before chill time for four days was used for two

19. Medical Research Council (footnote 16 *c*).
20. Acton, Sinton and Bird (footnotes 16 *b* and 16 *e*).
21. Hegner, R.; Shaw, E. H., Jr., and Manwell, R. D.: Methods and Results of Experiments on Effects of Drugs on Bird Malaria, Am. J. Hyg. **8**: 564 (July) 1928.
22. Sanders (footnote 2 *b*).

reasons. First, it was the method used in the 39 cases in which quinidine was administered, and, second, in such small quantities we thought any difference between the two drugs might be accentuated.

The observations in 1931 on quinidine and quinine were carried out in 125 patients with malaria treated by one of us (J. P. S.) at Caspiana, La. In the course of a country general practice, 61 patients were treated with quinine, 64 with quinidine, mostly in alternate cases. Treatment consisted of one 10 grain dose of quinine or quinidine sulphate, generally in capsules, on each of four consecutive days, each dose being given about three hours before the hour of the chill in the particular case. Treatment was ordered as soon as the clinical diagnosis of malaria was made. At the same time a blood smear was made and forwarded to Dr. W. J. Sandidge, of the Caddo Parish Health Unit at Shreveport, for definite diagnosis. More than a third of the patients had negative blood smears and are, therefore, excluded from further consideration here.

How were we justified in trusting that so little treatment would secure the safety of the patient? The answer lies in the history of the subject. Wade,[15] in 1868, reported on the treatment of malaria usually with single 10 grain doses in solution. He treated 300 patients with quinidine and found one dose sufficient in 268 cases, two needed in 30 cases and three doses in 2 cases, "to stay the attack of fever." Results with quinine were similar. Giemsa and Werner [1] obtained good results in malaria with 0.2 Gm. (3 grains) of quinidine hydrochloride twice daily. Stephens [23] and his collaborators showed that in chronic benign tertian malaria a 10 grain dose of quinine sulphate on each of two successive days caused temporary cure and absence for ten to eighteen days of parasites from the peripheral blood.

By excluding patients with initial negative blood smears, the clinical material for consideration is reduced to fifty-one patients with benign tertian malaria and thirty-two with estivo-autumnal infection, a total of eighty-three cases. In considering them it should be remembered that these patients were liable to reinfection, though the area involved is not considered heavily infected. In the follow-up work on these patients the demands of country practice sometimes caused difficulty in securing blood smears at times desired. With the aid of a nurse follow-up smears were eventually made on most of the patients in the fall of 1931 and spring of 1932, and by this means we have been able to list a number of "cures," meaning by this patients who without further treatment, so far as could be learned, remained well a hundred days and showed after this time a negative blood smear. Relapse may occur in malaria even later than this, but a relapse could not in any case be distinguished from a reinfection. Negative blood smear does not, of course, exclude presence of parasites in the body.

The results are shown in the table, and may be briefly summarized as follows: Quinidine sulphate in dose of 10 grains once daily for four days caused abrupt termination of the chills so that only four of forty patients had even one more chill after the first dose; no patient on quinidine had more than one. On quinidine the patients averaged less than two days of fever. The number of days to clinical recovery averaged less than six. The percentage of "cures" judged by absence of symptoms for a hundred days subsequent and a negative smear a hundred days or more later was 57 per cent in benign tertian malaria, and 47 per cent in estivo-autumnal infection. Because of the difficulty of securing smears in some other cases in which "cure" might have been obtained in this sense these figures are probably low rather than high. It is astonishing that so high a proportion as 50 per cent should obtain with so mild a treatment, especially as these patients were liable to reinfection. Only four of forty patients required further treatment within thirty days. Twenty were Negroes.

Of the forty-three patients treated with quinine sulphate in similar dosage, all but two were Negroes, and supposed therefore by some to have more natural resistance to malaria, but twenty had one or more chills subsequent to beginning treatment; the days of fever averaged about four, and the days to clinical recovery just over ten. This seems to show quinidine a little superior, but one has to consider that quinidine sulphate is nearly ten times as soluble as quinine sulphate and contains a higher percentage of alkaloid, about 82 against 73 per cent in quinine sulphate. These factors may help to account for the slightly better results from quinidine. With quinine seven of forty-three patients required further treatment within thirty days.

In 104 cases in which quinidine was used in the years 1930-1931, a case was noted of slight cardiac irregularity, occurring an hour or so after the dose, and not recurring if the patient stayed in bed. Two pregnant patients were given quinidine for malaria in the fourth and eighth month, respectively, without any ill effect to child or mother. No patient has complained of any ill effect from quinidine except the one previously mentioned, not even of cinchonism.

COMMENT

We are not advocating, except for experimental use, the method of treatment used in this series. The National Malaria Committee plan of treatment,[24] evolved largely from the data collected by Bass [25] on 25,000 cases, calls for 10 grains of quinine sulphate three times a day for three or four days and then once a day for eight weeks. Our results tend to support the conclusion that 30 grains a day in the initial stages is sufficient [26] to remove the danger of the acute attack in malaria. With 105 consecutive patients with positive smears, the plan of giving only one 10 grain dose a day of quinidine or quinine sulphate was rigidly adhered to. Many of these patients were severely ill; temperatures up to 106 F. were noted, and some patients were delirious. All took the alkaloid by mouth, usually in capsules, but in a few cases in solution.

In evaluating any method of treatment it must be borne in mind that in untreated malaria, as in many other diseases, while the outcome may be fatal, remissions, sometimes long, may spontaneously occur.[27] There is a natural resistance to the infection, varying with the individual. The mechanism involved is unknown. Quinine probably does not act directly on

23. Stephens, J. W. W.; Yorke, Warrington; Blacklock, B.; MacFie, J. W. S.; Cooper, C. Forster and Carter, H. F.: Oral Administration of Quinine for Two Consecutive Days Only in Simple Tertian Malaria, Ann. Trop. Med. **11**: 283 (Jan.) 1918.

24. Report of the Subcommittee on Medical Research of the National Malaria Committee, November, 1919, The Treatment of Malaria, Pub. Health Rep. **34**: 2959, 1919. Compare Sinton, J. A.: A Suggested Standard Treatment of Malaria Based upon the Results of the Controlled Investigation of Over 3,600 Cases, Indian M. Gaz. **65**: 603 (July) 1930.

25. Bass, C. C.: Studies on Malaria Control, II. The Treatment of Malaria, with the Special Object of Disinfecting Infected Persons, Adopted After Wide Experience in Malaria Control by Treating Malaria Carriers in the Mississippi Delta, J. A. M. A. **72**: 1218 (April 26) 1919.

26. Bass, C. C.: Specific Treatment of Malaria, New Orleans M. & S. J. **74**: 521 (Jan.) 1922.

27. Boyd, Mark F.: An Introduction to Malariology, Cambridge, Mass., Harvard University Press, 1930.

the parasite: whether it increases natural resistance or activates some special mechanism for destroying the parasites is unknown.[28] Yorke [29] and Sinton [30] find it conceivable that excessive dosage or prolonged administration of large doses may hinder cure; the plan used in the present series certainly does not err in that direction.

CONCLUSIONS

1. The antimalarial efficacy of quinidine is confirmed.
2. Trial of the drug in a total of fifty-seven cases of malaria with positive smears in a country practice in Louisiana in 1930 and 1931 has revealed no inferiority to quinine. Of these cases, thirty-three were benign tertian and twenty-four estivo-autumnal.
3. A 10 grain dose of quinidine sulphate once daily about three hours before chill time rapidly removed the acute dangers of malarial fever in all cases.
4. The same dose once daily for four days was effective and did no harm in two pregnant patients.
5. Quinidine is recommended for trial as a quinine substitute in cases of asthmatic, coryzal or urticarial reaction to quinine, or in cases of malaria in which the response to quinine is poor.

ABSTRACT OF DISCUSSION

DR. W. J. SANDIDGE, Shreveport, La.: In the northwestern section of Louisiana, where this work was done, conditions were favorable for doing the work. Many of the patients are plantation Negroes, who are living, for the most part, in unscreened homes. Malaria is fairly prevalent in the section and numerous bayous, ponds and small bodies of water furnish ideal breeding places for anopheles mosquitoes. These Negroes seldom move far and the doctor is in rather close contact with the patients most of the time. Except in a small percentage of cases, if the patient relapses, Dr. Sanders would know about it. He is in more direct contact with his patients than most city doctors. In plantation practice on the river sections, if a Negro doesn't get well, the planter wants to know about it and he gets in touch with the doctor. Thick smears were taken at the time clinical diagnosis was made. These thick smears were stained with Giemsa's stain. We felt that with this method we were able to find a higher percentage of positives than with the ordinary thin smear method. As every one knows, a negative blood smear does not necessarily mean that the patient has at that time no parasites in his blood. Follow-up slides and follow-up clinical histories were taken on a few of these cases by Dr. Sanders himself. A public health nurse from Shreveport took most of the follow-up slides and clinical histories. Part of the follow-up slides were taken in duplicate and one set sent to the United States Public Health Service Laboratory at Greenwood, Miss., as a check. The follow-up histories taken by the nurse were unbiased. Neither she nor, in most cases, the patient knew which alkaloid had been given. The nurse questioned closely as to the number of chills, days of fever, and number of days of convalescence after the initial dose. The percentage of error should be about equal in the two series of cases. A few patients cannot take quinine, because of an idiosyncrasy. When such patients contract malaria, they are a difficult problem. Arsenicals are poor substitutes for quinine in treating such cases. Plasmochin is probably dangerous in a small percentage of cases and is not effective in estivo-autumnal malaria. In the cases reported here, I am convinced that quinidine is at least equal to quinine in its antimalarial value. It occurs to me that cases of malaria resistant to quinine might possibly improve more rapidly under quinidine therapy.

28. Sollmann, T.: Manual of Pharmacology with Applications to Therapeutics and Toxicology, ed. 4, Philadelphia, W. B. Saunders Company, 1932.
29. Yorke, Warrington: Further Observations on Malaria Made During Treatment of General Paralysis, Tr. Roy. Soc. Trop. Med. & Hyg. **19**: 108 (Sept.) 1925.
30. Sinton, J. A.: Studies in Malaria with Special Reference to Treatment: XIV. The Effects of Dosage of Drugs and Duration of Treatment on Production of Cure, Indian J. M. Research **18**: 831 (Jan.) 1931.

Clinical Notes, Suggestions and New Instruments

AMPUTATION OF ARM OF PATIENT WITH HEMOPHILIA

ALFRED BLALOCK, M.D., NASHVILLE, TENN.

This report of the successful amputation of an arm of a patient with hemophilia is given because of the unusual difficulties that were encountered.

J. B. S., aged 39, entered the Vanderbilt Hospital forty-eight hours following an accident in which he was struck by a truck. He was unconscious most of the time between the accident and his admission to the hospital. Examination showed that the patient was extremely ill. The systolic blood pressure was 85 mm. of mercury and the diastolic 60. He was pale and sweating profusely. The right arm and hand were greatly swollen. There were ecchymoses in the region of the left wrist. The right hip was swollen and tender. Air was present in the soft tissues of the right side of the chest. Roentgen examination of the chest revealed fractures of seven ribs on the right side, three of the ribs being fractured in two places. Fluid was present in both pleural cavities.

The patient was given 600 cc. of salt solution intravenously immediately after entering the hospital. The systolic blood pressure rose to 100 but declined in a short while to the previous level. He was then given a transfusion of whole blood; the blood pressure became elevated and remained so for two hours, when again it declined to a low level. A second transfusion caused a sustained rise in the blood pressure.

Examination of the patient's blood shortly following admission to the hospital showed the clotting time to be thirty-five minutes. The red blood cell count was two million, the hemoglobin 45 per cent and the platelets 360,000. It was found on questioning relatives that the patient had almost bled to death on several occasions following minor injuries. Several of his joints had been swollen and painful at times. One brother and two maternal uncles died from hemorrhage. It was stated that the patient's maternal grandmother had spoken of relatives of hers who were bleeders, but information on this point was not definite.

The general condition of the patient was much improved the day following his admission to the hospital. The blood pressure was normal. The right arm and hand were greatly swollen and there was an absence of sensation and motion of the right hand. Two days later the swelling of the right upper arm and forearm had definitely lessened and beginning gangrene of the right hand was noted. A line of demarcation was present just above the wrist. The gangrene was at first of the dry type. Large blebs containing clear fluid later appeared on the right hand. Thirteen days following his admission to the hospital the clotting time was one hour and forty-five minutes. At that time the daily subcutaneous injection of an ovarian preparation obtained from the fetal fluid of cattle was begun. One week later the clotting time was two hours and five minutes. After the patient had been in the hospital four weeks the right forearm became red and swollen and the right hand bled slightly at each dressing. The temperature rose to 104 F. Three days later blood began to spurt from an artery at the base of the thumb. This was controlled by the application of a tourniquet above the wrist. The patient was then taken to the operating room.

The patient was prepared for an amputation across the midportion of the upper arm. This was performed under nitrous oxide-oxygen anesthesia supplemented by a small amount of ether. A tourniquet was not applied proximal to the site of the amputation as it was feared that this would result in hemorrhage into the compressed tissues. Hemostasis was procured by ligating with catgut ties previous to its division every bit of soft tissue excepting the skin. The bone and large vessels were divided at the same level as the skin, as it was feared that the freeing of them from the surrounding tissues would result in hemorrhage that could not be controlled. No attempt was made to close the skin over the end of the stump. At the completion of the operation there was a small amount of oozing from the

From the Department of Surgery of Vanderbilt Hospital.