The Use of Calcium Gluconate in the Treatment of Malarial Chills[1]

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ALTHOUGH THE INCIDENCE of malaria is rapidly diminishing in the Island of Puerto Rico, it is a well-known fact that this condition still holds first place among communicable diseases.[2] However, as the death rate has been relatively low (97 per 100,000 population), malaria holds sixth place among the leading causes of death.

Those who have suffered from malaria—and I quote from personal experience—claim that the worst symptom, by far, of this common tropical disease is the chill that usually precedes the fever. Anyone who has seen patients quaking in the throes of a hard-shaking chill, with knees drawn up, neck drawn forward, teeth chattering, head and body buried under all available covering that never appears to be enough, knows for sure that this statement is true. Those of us who have experienced malarial chills swear to it as a certainty.

Chills have been mentioned as a sign of disease since the earliest medical writings, and throughout the course of medical and literary history one finds frequent reference to this phenomenon. The word "ague," signifying the recurrent chills and fever of malaria, has been used for many centuries. However, in spite of the importance and frequent occurrence of chills in malaria and in many other pathological conditions, it has been only during recent years that this manifestation of disease has been studied from the physiologic standpoint. Richet,[3] fifty years ago, described chills as a combination of a subjective perception of inward trembling or actual cold, and a more or less generalized involuntary muscle tremor, visible as an objective sign. Recently Perera,[4] in his splendid paper on the clinical and physiologic characteristics of chills, described them as "a combination of both subjective and objective bodily changes,

1. Received for publication September 27, 1943.

2. Report of the Commissioner of Health to the Honorable Governor of Puerto Rico for the Fiscal Year 1940–1941 (San Juan, P.R.: Bureau of Supplies, Printing and Transportation).

3. C. Richet, cited by George A. Perera, "Clinical and Physiologic Characteristics of Chill," *Arch.Int.Med.*, 68:241, 1941.

4. G. A. Perera, *op. cit.*

varying in intensity from a tremulous feeling, or a sensation of cold, to a violent widespread shivering or rigor."

In general, chills may be due to external causes (as exposure to cold) or to internal causes (as bacterial invasion). When an external factor for increased heat loss is present, shivering serves as an important mechanism in temperature regulation by increasing heat production through muscular contractions. The following teleologic theory of the physiology of chills has been proposed by most modern students to explain their occurrence in disease: there is considerable evidence to the effect that there exists a thermostatic center located in the posterior portions of the hypothalamus; that this center may be stimulated by the toxic agents elaborated in certain diseases and thus be set to a higher level, shivering then occurring as a means of raising the body temperature to this new thermostatic level.

Chills may occur at any period of life and have been observed in a twenty-five-month-old child and in patients eighty years of age. In infants convulsive movements may be the equivalent of chills. Although it is difficult to decide just when chills start because verification of this fact depends on the patient's reliability as an observer, it is known that they may last from a few minutes to over three hours.[5] The average duration in Perera's cases was forty-three minutes; in his cases the longer the duration of the chill, the higher was the ensuing temperature. The duration of chills[6] is usually in inverse proportion to the amount of subcutaneous fatty tissue as recorded by body weight, fat people having shorter chills than lean ones. A chill is usually accompanied by a steady rise of rectal temperature;[7] the cutaneous temperature is reduced in most cases but may remain unchanged in some.

The following are the main physiologic changes known to occur during a chill: slower heart rate, irregular respiratory rate, and rising blood pressure. There is a constant drop in the white blood cell count, and for this reason white blood cell counts should not be made during a chill, as the discovery of a leukopenia may give rise to a false diagnosis. The hematocrit reading rises with severe chills. The specific gravity of the urine usually falls. Chemical studies of

5. G. A. Perera, *op. cit.*

6. R. W. Swift, "The Influence of Shivering, Subcutaneous and Skin Temperature on Heat Production," *J.Nutr.*, 5:277, 1932.

7. W. F. Petersen and E. F. Müller, "The Splanchoperipheral Balance During Chill and Fever," *Arch.Int.Med.*, 40:575, 1927.

the blood reveal no significant changes in most cases. The muscles display increased tonicity, the muscle tremor being rhythmical in nature and the rate of tremor varying from four to seven per second.[8] Although the tremor of the chill is involuntary in nature, some degree of voluntary control can be exercised in milder cases. Surprisingly, the tremor that accompanies a chill is not followed by exhaustion.

The general opinion seems to be that a chill generally accompanies the fever in malarial paroxysms. However, in a careful study of four hundred and twenty febrile paroxysms in induced malaria during the treatment of neurosyphilis, Young and his collaborators[9] found chills occurring in only 24 percent of their cases. Our experience has been that the febrile phase is not necessarily preceded by a chill, as in the classical description, but that more than half of the patients admitted with malaria do have chills, or give a history of having experienced chills during febrile paroxysms.

Because of its location in a well-known malarial district, the Fajardo District Hospital has furnished innumerable opportunities to study the clinical picture of such chills. Thirty percent of all admissions to the medical wards of this hospital during the fiscal year 1940–1941 were cases of malaria,[10] and it was rather embarrassing not to be able to offer the symptomatic relief for which these patients clamored, at times even in preference to the specific treatment of the disease. It was therefore a real satisfaction to read the reports of Beeson and Hoagland[11] on the successful treatment of chills with intravenous calcium chloride in three patients suffering from induced malaria in the treatment of neurosyphilis. They had previously reported the prompt termination of the chills occurring after blood transfusions and after the intravenous injection of typhoid vaccine and antipneumococcic serum.[12] Their account induced us to give calcium a more extensive clinical trial in malarial chills.

8. G. A. Perera, *op. cit.*

9. Martin D. Young, G. Robert Coatney, and Sol B. McLendon, "Studies of Induced Quartan Malaria in Negro Paretics. III. Measurements of the Paroxysmal Phases," *Southern Med.J.*, 34:709, 1941.

10. Second Annual Report of the Director, Fajardo Charity District Hospital, to the Honorable Commissioner of Health of Puerto Rico for the Fiscal Year Ending June 30, 1942.

11. Paul B. Beeson and Charles L. Hoagland, "The Use of Calcium Chloride in the Treatment of Chills," *New York State J.Med.*, 40:803, 1940.

12. Paul B. Beeson and Charles L. Hoagland, "The Use of Calcium Chloride in the Relief of Chills Following Serum Administrations," *Proc.Soc.Exp.Biol.& Med.*, 38:160, 1938.

SELECTION OF CASES AND MODE OF PROCEDURE

All cases of malaria, proved as such by blood smear and admitted to the medical wards, which gave a history of chills prior to admission and whose condition was not serious enough to constitute a contraindication, were selected as presumptive candidates for this experiment. Antimalarial treatment was withheld. During the routine examination the duration of previous chills was ascertained and recorded. The patient was told to be on the alert for the first sign of an oncoming chill and instructed to report it immediately. The time of onset of the chill, according to the patient's report, was recorded.

The character of the chill was also recorded according to the following scheme:

(a) One-plus intensity—for cases with chilly sensations, feeling of coldness, and any other subjective symptoms without objective signs.

(b) Two-plus intensity—for cases with shivering, slight tremor, and shuddering that required blankets.

(c) Three-plus intensity—for cases where there was some shaking with chattering of the teeth and trembling.

(d) Four-plus intensity—for hard-shaking chills with quaking, marked chattering of the teeth, and shaking of the entire bed.

It was decided to use calcium gluconate rather than chloride salt of calcium because of less danger in tissue sloughing at the site of venipuncture. The fact that it had been definitely proved that calcium chloride, given orally or intravenously to animals, was more toxic,[13] also weighed in favor of our selection.

As soon as possible after onset of the chill, and after careful venipuncture, 10 cc. of a 10 percent solution of calcium gluconate was administered very slowly. This procedure was at times difficult because of the uncontrollable shaking of the patient. The time was again recorded at the end of the injection.

Before injection the patient had been instructed to describe any subjective sensations he might experience, particularly in regard to diminution of the degree of chilliness, and to report the disappearance of the chill at once. This was checked by observation of the objective signs of the chill and the approximate duration of the latter

13. Elizabeth R. B. Smith, "Comparison of Effects of Large Doses of Calcium Gluconate-Iodonate, Calcium Gluconate, and Calcium Chloride," *J.Lab.& Clin.Med.*, 25:1018, 1940.

was then recorded. All untoward signs and symptoms, arising at the time of the injection and afterwards, were also recorded. The patient was instructed to report any recurrence of a chill after it had been relieved by the injection.

RESULTS AND DISCUSSION

Fifty trials were carried out on forty patients. The results obtained are tabulated in detail in the accompanying table.

In only two of the fifty trials (5 and 33) did the calcium fail to have an observable effect. It must be noted that in Case 5 the chill had lasted for about half an hour before the injection was administered. In a second trial on this same patient, when the chill was treated within less than a minute of its onset, astounding results were obtained and complete relief was experienced in thirty seconds. The chill had lasted approximately one and a half hours in Case 33. A second trial on the same case, when calcium was administered about three minutes after onset of the chill, resulted in complete relief in three minutes more. Obviously, in computing averages we have not included these two cases as we considered that calcium was not given an opportunity in the original two trials. These findings led us to conclude that, in order to be effective, calcium should be given as soon as possible after onset of the chill; apparently, the sooner it was administered, the quicker were the results obtained. As proof of this (Fig. 1), we found that all cases treated within five minutes after onset of the chill showed complete relief within 3.7 minutes post injection, while in cases in which the injection was administered five or more minutes after onset, the chill had an average duration of 9.7 minutes.

The best results were obtained in the following six cases that showed a very astounding and prompt response: Case 13, complete relief in fifteen seconds; Case 6, in thirty seconds; Case 18, in forty-five seconds; Case 20, in thirty-five seconds; Case 27, in twenty seconds, and Case 25 had complete relief in fifty seconds. The average duration of all chills after treatment was 7.2 minutes (Fig. 2).

A review of the duration of previous untreated chills recorded in the histories showed three cases in which they had lasted approximately three hours. The shortest had a duration of ten minutes, while the average duration had been one hour, 13.5 minutes. We have calculated the expected duration of the chill—had calcium not been given—by subtracting the time elapsed before calcium administration from the duration of the previous chills as given by the patient in his history (assuming that the patient's succeeding chill would have been comparable in length with the one recorded in the history). The average duration, if calcium had not been effective, would have been 64.1 minutes, as compared to the actual average duration of the chill after calcium administration of 7.2 minutes (Fig. 2). This last figure provided a true basis for comparison between what would have been expected—had calcium not been effective—and the actual results.

No relation was found between the type of plasmodium and the response to therapy. Although most of the cases were vivax infections, there were five falciparum cases and four mixed infections. They all responded equally well to therapy.

Of the fifty chills treated, following classification as to intensity, twenty-eight were of 4+ intensity, fourteen of 3+ intensity, and eight of 2+ intensity. All cases of two and three plus intensity had complete relief within variable periods of time. Six of the cases with 4+ intensity (7, 8, 22, 26, 38, and 47) did not show the usual response. Four of them (7, 22, 26, and 38) had complete relief within a fairly short time, but such relief lasted only a few minutes when the chill reappeared with diminished (2+) intensity and continued for periods varying from two minutes to one hour, before disappearing completely. Two other cases of 4+ intensity (8 and 47) showed an almost immediate diminution of the chill to a 2+ intensity that was finally completely relieved in fifteen and ten minutes, respectively.

In the fifty trials performed, only fourteen patients complained of untoward effects. These occurred as follows: nausea and vomiting, 4; headache, 6; oppression over the chest, 1; epigastric discomfort, 1; flushing of the face, 1; dizziness, 1. However, none of these symptoms was so severe as to make us feel that calcium gluconate should not have been utilized.

It is generally believed that at the time of rupture of the infected red blood cells, in malarial infections, there is released into the blood stream a specific toxinlike substance that is responsible for the production of the ensuing paroxysm of chill and fever. No definite proof of this has been presented.[14] However, since it is a well-established fact that red blood cells contain twenty times as

14. S. F. Kitchen, "The Morphology, Life Cycle and Physiology of *Plasmodium falciparum*," The American Association for the Advancement of Science, Pub. 15, pp. 41–46.

much potassium as the plasma, it is possible that potassium may be the responsible toxic substance.

With this hypothesis in mind, Zwemer, Sims, and Coggeshall[15] studied the potassium level both in monkeys and man during malarial infection and found that potassium values gradually increased with each cycle, the peak occurring at the onset of the chill in man. Pinelli[16] found elevated plasma potassium in malaria during paroxysms with return to normal during afebrile phases. Crosetti,[17] investigating hemolytic anemias, including malaria, found an elevation of the potassium level that was in relation to the amount of hemolysis, and considered it an index of hemolysis. It is a well-known clinical fact that acute hemolytic episodes, such as seen in blood transfusion reactions, sickle cell anemia, congenital hemolytic icterus, and so forth, are accompanied at the onset by hard-shaking chills, usually followed by fever. This also points to potassium as the causative agent in the production of these particular paroxysms.

If so, the use of calcium, whose physiologic action is known to be antagonistic to that of potassium, would seem to be well indicated on a theoretic basis. However, there are several known facts opposed to this plausible theory: (1) although investigators have found a marked increase in the potassium level of monkeys with malaria, these animals never develop chills; (2) experimental alterations of potassium levels by intravenous injection have been found difficult to obtain, the potassium regulating mechanism being extremely efficient and such alterations as were produced not being accompanied by chills.[18] On the other hand, it is generally known that calcium salts, when given intravenously, produce a sensation of warmth throughout the body. It may be that this warmth-producing property may be enhanced in the presence of chills and, therefore, instrumental in their rapid termination.

Although reports of serious toxic effects from the therapeutic use of calcium gluconate, intravenously, are uncommon, the following precautions are nonetheless recommended:

(a) Venipuncture should be carefully carried out, since extravasation of the calcium solution into the subcutaneous tissues may be followed by necrosis.

(b) The injection should be given slowly.

(c) The patient should remain recumbent for about fifteen minutes after the injection.

(d) The use of intravenous calcium is definitely contraindicated in most cardiac cases, particularly those with arrythmias and bradycardia, because of the initial vagus stimulating effects that may cause marked slowing down of the cardiac rate. However, some claim that no real danger exists, if the calcium is given slowly.[19]

(e) It is also contraindicated in patients who are receiving digitalis therapy, as calcium and digitalis have an additive, or synergistic, effect on the heart.[20]

15. R. L. Zwemer, E. A. Sims, and L. T. Coggeshall, "The Plasma Potassium Level during Malaria Infection in Monkeys and Man," *Am.J.Trop.Med.*, 20:687, 1940.

16. L. Pinelli, cited by Zwemer *et al.*, *op. cit.*

17. L. Crosetti, cited by Zwemer *et al.*, *op. cit.*

18. W. Winkler, H. E. Hoff, and P. K. Smith, "Electrocardiographic Changes and Concentration of Potassium in Serum Following Intravenous Injection of Potassium Chloride," *Am.J.Phys.*, 124:478, 1938.

Normal M. Keith, Arnold E. Oterbery, and Howard B. Burchell, "Some Effects of Potassium Salts in Man," *Collected Papers of the Mayo Clinic and Mayo Foundation*, 33:967, 1941.

SUMMARY AND CONCLUSIONS

By far the most uncomfortable symptom of malaria, from the standpoint of the patient, is the chill that usually precedes the fever. In an attempt to relieve these chills, a clinical trial was conducted in fifty cases of malaria, using calcium gluconate intravenously. Very satisfactory results have been obtained in most cases, with but few and mild untoward symptoms recorded.

Intravenous calcium gluconate, when given soon after the onset of the chill, produces a complete termination of the phenomenon within one to three minutes, in most cases.

A few considerations as to the pathologic physiology and probable mechanism of chills, in general, and malarial chills, in particular, have been presented.

19. A. J. Espinosa de los Monteros and J. Lozano López, "Acción del calcio sobre el corazón del hombre normal," Extracto de *Los Tratamientos Actuales*, No. 130, 1936.

20. J. O. Bower and H. A. K. Mengle, "The Additive Effect of Calcium and Digitalis," *J.A.M.A.*, 106:1151, 1936.

P. K. Smith, A. W. Winkler, and H. E. Hoff, "Calcium and Digitalis Synergism. The Toxicity of Calcium Salts Injected Intravenously into Digitalized Animals," *Arch.Int.Med.*, 64:322, 1939.

Results Obtained in the Treatment of Chills with Intravenous Calcium Gluconate

Name	Unit No.	Type of Malaria	Duration of Previous Chill	Intensity	Duration of Chill before Injection	Duration of Chill after Injection	Remarks
1. J.M.F.	7070	*P. vivax*	No history obtained	4+	15 min.	3 min.	Complete relief
2. J.M.P.	7414	*P. vivax*	No history obtained	4+	Not recorded	3½ min.	Complete relief
3. R.G.	7459	*P. vivax and falciparum*	Not recorded	4+	Not recorded	1¼ min.	Complete relief
4. C.A.	7442	*P. vivax*	Not recorded	3+	10 min.	5 min.	Complete relief
5. J.R.	7217	*P. vivax*	No previous chill	4+	About ½ hr.	Chill cont. about ½ hr.	Therapeutic malaria in case of C.N.S. lues. No response in chill of long duration, but astounding result when treated immediately after onset of chill
6. J.R.	7217	*P. vivax*	Over 1 hr.	4+	Less than 1 min.	30 sec.	Chill of 2+ intensity reappeared, lasting 1 min.
7. F.G.	6324	*P. vivax*	No previous chill	4+	25 min.	2 min.	Chill diminished immediately to 2+ post injection
8. R.R.	7809	*P. vivax*	Used to last ½ to 1 hr.	4+	About ½ hr.	15 min.	Complete relief
9. R.R.	7809	*P. vivax*	Used to last ½ to 1 hr.	4+	20 min.	10 min.	Complete relief
10. R.R.	7809	*P. vivax*	Used to last ½ to 1 hr.	3+	2 min.	10 min.	Complete relief
11. C.E.	7805	*P. vivax*	Not recorded	2+	1 to 2 min.	5 min.	Complete relief
12. E.L.	7840	*P. vivax*	Used to last about 1 hr.	3+	4 min.	5 min.	Complete relief
13. C.de J.	7864	*P. vivax*	Used to last from 1 to 2 hrs.	3+	5 min.	15 sec.	Complete relief
14. J.R.	7857	*P. vivax*	About 1 hr.	4+	About 5 min.	30 min.	Nausea and sense of oppression over chest
15. P.M.	2766	*P. falciparum*	About ½ hr.	4+	5 min.	7 min.	Complete relief
16. L.M.	8021	*P. vivax*	Over 1 hr.	3+	10 min.	9½ min.	Complete relief
17. L.M.	8021	*P. vivax*	Over 1 hr.	3+	3 min.	5 min.	Complained of headache and epigastric discomfort
18. J.R.C.	8028	*P. vivax*	About ½ hr.	3+	3 min.	45 sec.	Complete relief
19. M.F.	8244	*P. vivax*	Over 1 hr.	4+	15 min.	4¼ min.	Complete relief
20. A.D.R.	2725	*P. vivax*	About 15 min.	2+	8 min.	35 sec.	Complete relief
21. G.R.	6465	*P. vivax and falciparum*	Over ½ hr.	4+	2 min.	1 min.	Flushing of the face immediately after injection
22. M.M.S.	7680	*P. vivax*	Over 1 hr.	4+	15 min.	30 sec.	Free of chills for 35 sec. followed by 2+ chills that occurred for 12 min. at intervals
23. M.M.S.	7680	*P. vivax*	Over 1 hr.	4+	12 min.	2½ min.	Nausea and vomiting after injection
24. I.C.	8602	*P. falciparum*	From 10 to 12 min.	3+	1 min.	1 min.	Complete relief
25. A.C.	8832	*P. vivax*	About ½ hr.	2+	2 min.	50 sec.	Metallic taste after injection

Results Obtained in the Treatment of Chills with Intravenous Calcium Gluconate—Continued

Name	Unit No.	Type of Malaria	Duration of Previous Chill	Intensity	Duration of Chill before Injection	Duration of Chill after Injection	Remarks
26. J.B.	8666	*P. falciparum*	Over 1 hr.	4+	5 min.	1 min.	Free of chills for 2½ min., followed by 2+ chill for about 1 hr.
27. M.A.	5630	*P. vivax*	No previous chill	3+	5 min.	20 sec.	Nausea, vomiting and headache 1 min. after injection
28. B.A.	9006	*P. vivax and falciparum*	No previous chill	4+	About 3½ hrs.	2¼ min.	Complete relief
29. S.A.	9021	*P. vivax*	About 3 hrs.	3+	6 min.	30 min.	Complete relief
30. S.A.	9021	*P. vivax*	About 3 hrs.	4+	7 min.	30 min.	Complete relief
31. M.F.	8821	*P. vivax*	No previous chill	4+	5 min.	25 min.	Complete relief
32. M.F.	8821	*P. vivax*	No previous chill	4+	4 min.	10 min.	Complete relief
33. J.A.	9283	*P. falciparum*	From 2 to 3 hrs.	2+	1½ hrs.	No effect	No effect after two doses of calcium
34. J.A.	9283	*P. falciparum*	From 2 to 3 hrs.	2+	3 min.	3 min.	Complete relief
35. J.M.	9467	*P. vivax*	About ½ hr.	4+	6 min.	15 min.	Nausea and headache
36. F.T.	2669	*P. vivax*	From 2½ to 3 hrs.	4+	About 1 hr.	15 min.	Complained of headache
37. M.L.	9621	*P. vivax*	From 1½ to 4 hrs.	3+	6 min.	5 min.	Complained of slight headache
38. F.M.	7719	*P. vivax*	About 3 hrs.	4+	Over ½ hr.	15 sec.	Free of chills for 1 min. followed by 3+ chill for 4 min.
39. R.J.	9430	*P. vivax*	From 2 to 3 hrs.	3+	4 min.	8 min.	Complete relief
40. R.J.	9430	*P. vivax*	From 2 to 3 hrs.	2+	12 min.	6 min.	Complete relief
41. J.M.	5963	*P. vivax*	From 15 to 30 min.	4+	3 min.	4 min.	Vomiting after injection
42. J.M.	5963	*P. vivax*	From 15 to 30 min.	4+	5 min.	3½ min.	Slight nausea after injection
43. M.T.	9053	*P. vivax*	From 1½ to 2 hrs.	3+	5 min.	5 min.	Nausea and vomiting after injection
44. J.M.	7229	*P. falciparum*	Not recorded	4+	5 min.	10 min.	Extremely severe chill with complete relief
45. F.M.	8902	*P. falciparum*	No previous chill	4+	Over 10 min.	15 min.	No effect 5 min. after first dose; complete relief following second dose
46. R.E.	11870	*P. vivax*	About ½ hr.	3+	4 min.	1 min. 35 sec.	Excellent response; patient felt slightly dizzy
47. M.F.	12284	*P. vivax*	No previous chill	4+	Over 5 min.	10 min.	Became of 2+ intensity immediately after injection
48. S.C.	12457	*P. vivax and falciparum*	About ½ hr.	4+	1 min.	2 min. 20 sec.	Slight nausea
49. G.G.	13222	*P. vivax*	No previous chill	2+	3 min.	1 min.	Complained of headache
50. M.R.	13629	*P. vivax*	Not recorded	2+	16 min.	2 min.	Complete relief

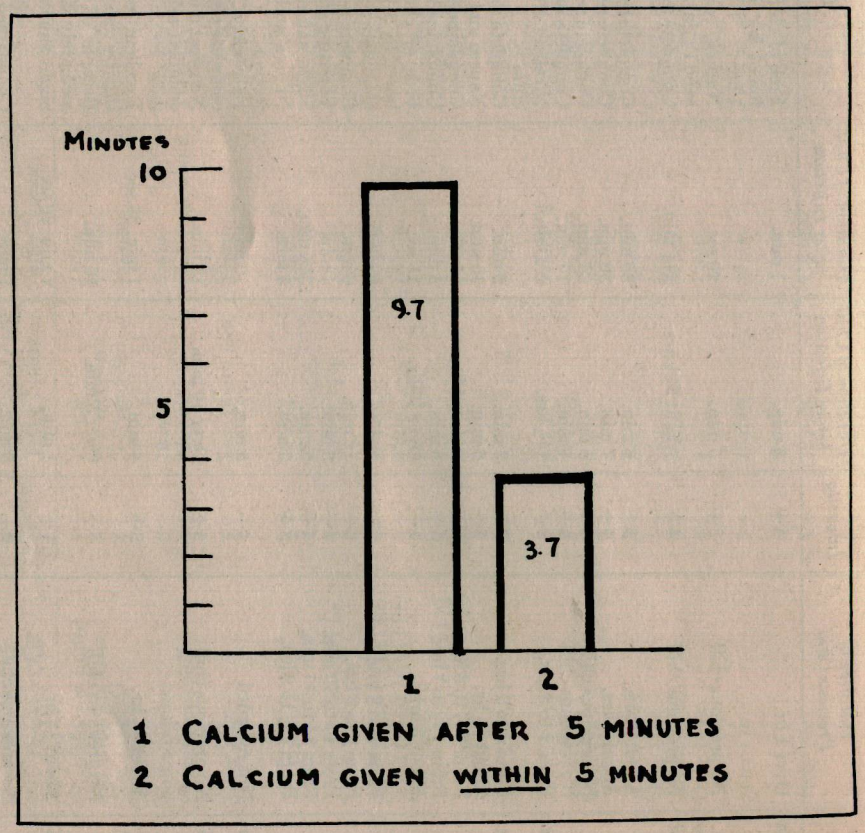

FIGURE 1
Advantage of Early Administration of Calcium

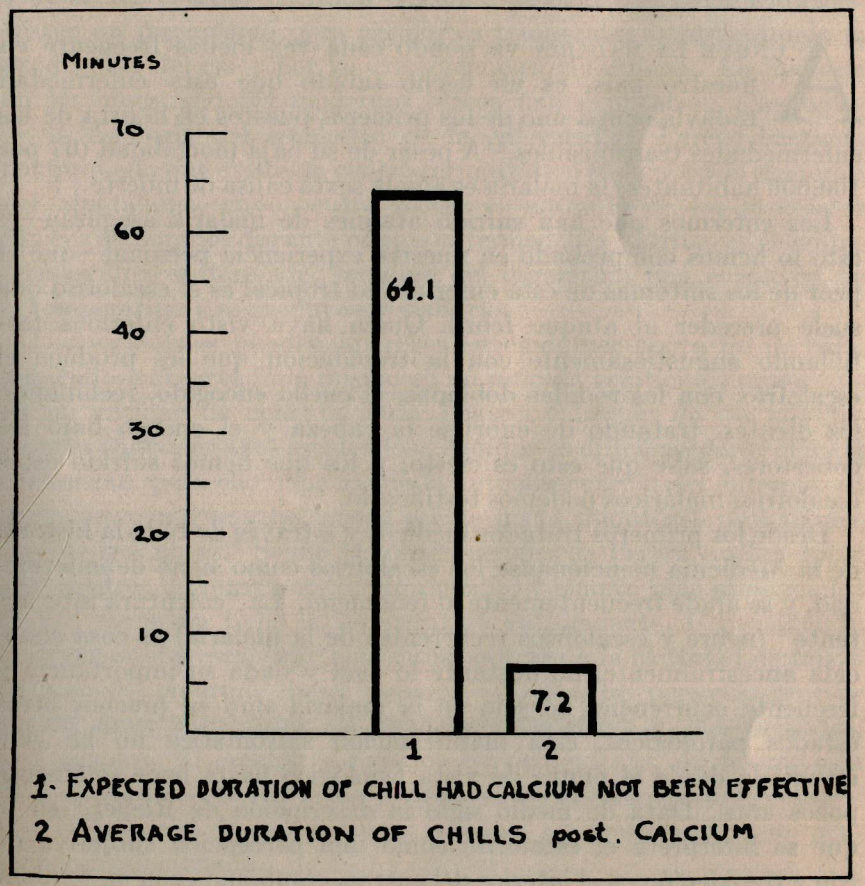

FIGURE 2
Duration of Chills