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First Paper

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S. T. DARLING, M.D., and W. G. SMILLIE, M.D.

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STUDIES ON HOOKWORM INFECTION IN BRAZIL.*

FIRST PAPER.

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INTRODUCTION.

Problems Studied.

The problems studied in relation to hookworm disease in Brazil during the year 1919 have been developed from two points of view. First, the special problems of Brazil—the degree of infection of the native Brazilian with hookworms, the geographical distribution of the disease, the variation of infection of individuals in various occupations and different standards of life, and the influence of race, as well as the study of the importation of hookworms by immigrants. The distribution of *Ankylostoma* and *Necator* has received special attention.

Second, problems of general interest in relation to the improvement and standardization of a routine method of hookworm treatment upon a large scale in the field. The points receiving special attention are: (1) The value of the microscope in routine field treatment, in (*a*) the preliminary diagnosis of hookworm disease, and (*b*) as an index of cure after treatment. (2) The efficiency of two routine field treatments of chenopodium by the hookworm post nurse. (3) The efficiency of a new method of treatment of hookworm infection with beta naphthol. (4) Studies of the best methods of administration of routine chenopodium treatment,—under hospital or dispensary conditions and under field conditions. The two specific problems considered were: (*a*) The value of the preliminary purge in the routine chenopodium treatment, and (*b*) the value of *division of the dose* in routine chenopodium treatment. (5) The toxicity of chenopodium.

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Material Utilized.

The requirements for the careful study of the more important general problems of hookworm disease are difficult to attain. The group of individuals should be under good discipline, and must also be willing to cooperate in the experiment. They must have sufficient intelligence to carry out directions and must be isolated from their fellows for at least 48 hours. All ages and equal numbers of both sexes should be chosen, and all stations of life should be included in the group. It has not always been possible to fulfill all these requirements. For example almost no children under 8 years of age have been included in the studies because of their lack of intelligence and discipline. In almost every instance in which we attempted to study children some of the stools were thrown away and the result of the work lost. In several instances carefully studied adult cases were thrown out of the series on the last day of the experiment, because they broke discipline and lost some of their stools.

The most satisfactory experiments have been carried out on large coffee plantations in isolated communities, for the colonists are under strict discipline and the plantation owners have been heartily cooperative. Almost all our work has been carried out in connection with The Rockefeller Foundation field hookworm posts, and we are greatly indebted to the whole staff of these posts for their assistance in the work. We are particularly indebted to Dr. L. W. Hackett, Dr. John L. Hydrick, and Dr. Mario Pernambuco for arranging locations in which to work, and loaning us nurses to assist in the worm counts. Dr. Allan Gregg spent 1 month with us in the field and was of valuable aid in carrying through three groups of experiments.

Methods Used.

The methods used in these studies have followed closely those devised by the Malaya Board (1) and also those used by us during the experiments of last year. The "trial treatment" is the experiment, and varies according to the factors that are to be studied. When a community has been chosen for the experiment a large number of individuals are registered and their hemoglobin estimations made by the Dare apparatus. From this number a representative group is

chosen, usually 28 or 30 persons, two-thirds or more being adults over 15 years of age and one-third children from 8 to 15 years. Records are kept for each individual containing the name, age, race, sex, occupation, hemoglobin, whether the spleen is palpable or not, previous anthelmintic treatment, previous malaria, and the result of the preliminary microscopic examination of the stools. Each patient is tagged with a number on the wrist and is given a urinal which has the same number. During the treatment careful records are kept of the hour of administration and the amount of the purge, dosage of the anthelmintic and the time when treatment was given, and all symptoms experienced, however trivial.

The entire stools are saved in the numbered urinal for 24 hours after treatment, when the patient is given a second urinal in which he saves his stools for another 24 hours. The stools are carefully washed on the day received, through a No. 40 copper gauze, all worms picked out, counted, and classified. Classified records of the worm counts of each individual are kept as follows: *Ankylostoma duodenale*, males and females; *Necator americanus*, males and females; *Ascaris*, males, females, and immature forms; *Trichocephalus; Oxyuris; Tœnia;* and other intestinal parasites that are sometimes removed.

Besides these data as to each individual, a short general description is given of the topographical characteristics of the location, as well as the general type of occupation, the standard of living, and a brief malarial survey. Finally a general summary is made of the results obtained in each experiment.

10 or 15 days after the trial treatment, the test treatment is given to determine the total number of hookworms remaining in the group. This interval should be allowed for the entire excretion of the drug administered in the trial treatment. The test treatment is always the same. A preliminary saline purge is given at 8 o'clock on the evening before treatment. On the following morning 1 cc. of chenopodium is given at 7, 8, and 9 a.m. on a fasting stomach, and a final purge is given at 10.30 a.m. The stools are saved for 24 and 48 hours, washed, the worms picked out, counted, and classified. $1\frac{1}{2}$ cc. of chenopodium are given to the children. When the experiment is carried out to determine merely the index of infection or the type of worm harbored the trial treatment is omitted.

The purge which we used in all experiments is magnesium sulfate, in 60 per cent solution. 20 to 40 gm. of the salt are given depending upon the age and the physical condition of the individual. Castor oil has been used only when the patient has been unable to retain the saline purge.

The chenopodium is administered in freshly prepared hard gelatin capsules, the dose being measured with standard graduated pipette. The capsules of chenopodium were all prepared, and were always administered by the same individual in all the experiments. The stools have all been washed by a single individual, a well-trained, careful, and conscientious technician, and though we have had assistance in picking hookworms from the washed stools, these stools are never discarded until they have been passed in final review before the director of the experiment. All worm counts and classifications have been made by one individual. The technique is not difficult but requires constant vigilance, painstaking care, great patience, and considerable experience.

Interpretation of Results.

We have accepted throughout this work the assumption that the test treatment of 3 cc. of chenopodium for adults and $1\frac{1}{2}$ cc. for children removes all hookworms. All our comparative results, in fact all our conclusions, rest on this as a basis.

We fully appreciate that the test treatment is not an absolute index and that it would be possible to follow our cases that have been given the test treatment with a microscopic examination of the stools, and in possibly a very small percentage of them find hookworm eggs. Previous work by the Malaya Board and by us has shown, however, that 3 cc. of chenopodium administered by the method described above remove more than 99 per cent of all hookworms and we feel justified in saying that this is a very small margin of error and a very satisfactory relative index upon which to base comparative conclusions.

Our experiments have been carried out with greatest care, and under almost ideal conditions, and the efficiency of the chenopodium is very striking. We anticipate that results equal to those obtained

in our experiments will not be obtained in a routine field laboratory. We must remember that field conditions are not ideal conditions. The field hookworm post nurse does not always realize the importance of careful details in treatment, the full dose of chenopodium is not always received by the patient, and the cooperation of the patients is sometimes lacking. If the field laboratory staff is able to approximate closely the method of treatment that we have given, then results will be obtained which will vary very little from our results.

Methods of Comparison of the Efficiency of the Various Anthelmintics.

The results that have been obtained by different methods of treatment have been compared from various points of view. There are several important criteria by means of which the efficiency of a given treatment may be judged. In all comparisons we have considered them in the following order.

Percentage of Hookworms Removed.—The most valuable criterion in considering the efficiency of methods of treatment is the percentage of hookworms that the treatment has removed. We have not considered the differential efficiency in the removal of necators and ankylostomes in these experiments because many groups harbored so few ankylostomes that comparative statistics were of little value.

Percentage of Cures by the Microscopic Test.—This index of comparison is included because it is the criterion most commonly in use in the comparison of the efficiency of anthelmintics. We believe that our work of this year has shown that this index is not of great value.

Percentage of Cures as Revealed by the Full 3 cc. Chenopodium Test Treatment.—This index is calculated from the number of cases that yielded worms on trial treatment but no worms on the test treatment. This criterion is of considerable comparative interest for it shows the number of cases that are freed of their hookworms on the trial treatment. As we have already explained, it is not an absolute factor, since it is possible that some worms remain even after test treatment.

Average Number of Worms Remaining per Case after Trial Treatment.—This criterion of comparison is different from any of the above, and is determined by obtaining an average per case of the hookworms that are removed by the test treatment. It is of distinct value in

comparing anthelmintic efficiency of various trial treatments for it shows the average number of hookworms the trial treatment left behind in the intestines of the patient.

Average Number of Failures.—It is obvious that we must draw the line somewhere between the success and failure of a treatment. If a person harbors 100 worms and a trial treatment removed all but 3, the individual is not cured, but nevertheless we cannot call the treatment a failure. We have arbitrarily set the maximum number of 10 worms as a failure in treatment. The number could equally well be 8 hookworms or 12, but for purposes of comparison it is very fair to consider that an individual who has received a trial treatment of a vermifuge and still harbors 10 hookworms should be considered a failure in treatment. This comparative index is obtained therefore by calculating the percentage of cases in a given group which harbored 10 or more hookworms after trial treatment.

We have, therefore, five different criteria by which to judge the efficiency of a hookworm treatment. The relative importance of these different factors is a matter of judgment. Certainly the first one—the percentage of total hookworms removed—is of greatest value. The other four criteria vary somewhat in proportion to the degree of infection; that is to say, if two groups, averaging 250 and 100 hookworms each, are given the same treatment there would be fewer cures, a greater average number of worms remaining, and a greater number of failures in the 250 worm group than in the 100 worm group. At times in comparing two groups of treatment one criterion of comparison so nicely balances the others that it is difficult to decide which of the treatments are more efficient. In case of doubt the most important index is of course the percentage of total hookworms removed by the trial treatment.

In the following pages we give a brief description of the method of study of the various problems and a summary of each is given with discussion, including a comparative study of the results obtained. Finally a general discussion and summary of all work done is given, with our recommendations.

DEGREE OF HOOKWORM INFECTION IN VARIOUS PARTS OF BRAZIL.

The study of the degree of hookworm infection in different parts of Brazil has been continued from the work begun last year. The number of worms removed by the test treatment of 3 cc. of chenopodium given in the manner already described in the introduction, has been used as the index of infection. Hookworm counts have been made in twelve different widely scattered localities, under different topographical conditions, and individuals of all ages above 6 years; various conditions of life, various occupations, and various races have been studied. Approximately equal numbers of both sexes are included. A summary of all findings for the year is given.

Summary for the Year January 1 to December 31, 1919.

Total No. of cases upon which worm counts have been made....	387
No. of stool specimens upon which worm counts have been made.....	1,192
No. of cases treated to determine the degree of hookworm infection.....	281
Total No. of *Necator americanus* expelled in these 281 cases.....	43,079
" " " *Ankylostoma duodenale* " " " 281 "	1,060
" " " hookworms expelled in these 281 cases.....	44,139
Average No. of hookworms per case.....	157
" " " ankylostomes per case.....	3.7
Proportion of ankylostomes to necators.....	1:41

Summary of Results Obtained in Brazil since the Initiation of Our Work, April, 1918, to January 1, 1920.

Total No. of cases which have been studied.....	596
" " " stools in which hookworm counts have been made	1,940
No. of cases treated to determine the degree of hookworm infection.....	469
Total No. of *Necator americanus* expelled.....	62,554
" " " *Ankylostoma duodenale* expelled.....	1,369
" " " hookworms expelled.....	63,923
Average No. of hookworms per case.....	136.1
" " " ankylostomes per case.....	2.9
Proportion of ankylostomes to necators.....	1:45

The variation in average total hookworm counts in the various groups studied has not been striking. There is a good reason for this since the groups studied were all more or less similar in that they were composed largely of agriculturalists. The average hookworm count of 136.1 per case therefore does not represent the degree of infection of *all Brazil*, but of *rural Brazil*, including all ages above 6 years, about equal numbers of males and females, and including small towns and villages, as well as plantations.

In the groups which were composed exclusively of field workers, the infection rate was very high and strikingly constant, independent of the State, or nature of the soil. Thus a group of adult field workers in northern São Paulo averaged 223 hookworms per case, whereas different groups of field workers, of 25 to 30 individuals in each group, in western São Paulo averaged 176, 282, 212, and 254 hookworms per case. A group of individuals who lived in a small village in the State of Rio de Janeiro of which only part were field workers averaged 148 worms per case, whereas a group which worked on a near-by cattle farm and were divided between field workers, milkers, and cowboys, averaged 145 worms per case. Thus village and pastoral life tends to reduce the index of infection. One group consisted of Indians on a reservation, in the State of Matto Grosso. They averaged only 88 hookworms per case, but their life is pastoral rather than agricultural. There is a much wider variation in infection rate between different *stations of life* in the same location than there is of individuals of the same station of life in different locations. For example; plantation owners and their families have about the same infection rate regardless of the community; administrators of plantations, storekeepers, bookkeepers, and their families have more hookworms than the wealthy owners, and fewer than the overseers, and so on down the scale; the individuals who are closest to the soil having the heaviest infection. Of all cases studied, only ten were found with no hookworms at all, five being adults over 14 years, and five children under 14 years.

The distribution of *Ankylostoma duodenale* is interesting. In a typical Brazilian rural community composed of descendants of a mixture of negroes and Indians and Portuguese with little or no emigration or immigration, the *Ankylostoma duodenale* are almost entirely

absent. For example, in a typical old Brazilian plantation in Atibaia, São Paulo, the proportion of ankylostomes to necators was 1 to 197. In a former slave plantation of Rezende where many of the ex-slaves and their descendants still live, and where there is little immigration, the proportion of ankylostomes to necators was 1 to 105. On one of the active new coffee plantations of western São Paulo where there was much immigration of foreigners—Italians, Spaniards, and Japanese—the proportion of ankylostomes to necators was 1 to 46. In one interesting plantation there was the home settlement composed of a fixed population, almost all Brazilians, and here the proportionate rate of ankylostomes to necators was 1 to 108. Only 2 miles away on the same plantation was a colony now composed entirely of Italian and Spanish immigrants, though there had also been many Japanese 2 or 3 years before. Here the proportion of ankylostomes to necators for the whole group was 1 to 20.

One colony of Japanese studied was interesting in that their total average hookworm count was small, but the ankylostome count was very high. The average hookworm count in this colony of Japanese was only 84.2 hookworms per case, but the proportion of ankylostomes to necators was 1 to 10. Table I gives a summary of the group divided into those who have been in Brazil 4 years or more and those who have been in Brazil 2 years or less.

TABLE I.

Hookworm Counts of Japanese Colonists in Brazil.

Length of time in Brazil.	No. of cases.	Average No. of ankylostomes.	Average No. of necators.	Average No. of total hookworms per case.	Proportion of ankylostomes to necators.
4 to 8 yrs.....	8	2.3	233.0	235.2	1:98
2 yrs. or less.....	20	9.6	14.1	23.7	1:1.4

The table shows that, after 4 or more years residence in Brazil, the Japanese colonist not only gives up his Japanese dress, food, mode of living, and begins to accept those of Brazil, but he also gives up the ankylostomes of the mother country and assumes the worm picture of the adopted country. Undoubtedly also the Japanese and other foreigners are infecting Brazilian soil with *Ankylostoma duodenale* but apparently are receiving in return a much heavier infection with *Necator americanus*, than they had when in their old home.

VALUE OF THE ROUTINE MICROSCOPIC EXAMINATION OF STOOLS IN HOOKWORM TREATMENT IN THE FIELD.

The microscopic examination has been the pivot around which all the work of the field post laboratory has revolved. If a case gave a positive result with the microscope it was treated, if negative the case was closed. It was of course realized that the microscope was not infallible; nevertheless, when the customary rigorous examination as carried out in the routine laboratory procedure has been followed, the microscope has been regarded as the most reliable and best standardized of all the factors in the field treatment.

The work of the Commission in Java and Malaya throws some suspicion upon the results obtained by routine laboratory microscopic examinations in the field, and in order to clarify this matter the following series of experiments were undertaken.

Experiment 1.—Fazenda Jabotical was a typical coffee plantation in a zone of moderately severe hookworm infection. The people of the plantation were registered in the routine way by the nurse and all received a routine microscopic stool examination by the microscopist of the field post. Without any previous warning, the post physician was then advised that we desired to give a test treatment to all cases on the plantation that were negative to the microscope, and to count their worms, which was done forthwith. Of a total population of 69 people on the plantation, 44 were positive and 25 negative by microscopic examination. 4 of the negatives were not treated because they were 2 years of age or less. Of the remaining 21 cases which were treated (Table II), there were 11 adults over 14 years of age and 10 children. 6 adults who were positive to hookworm infection by the microscopic examination were treated as controls.

The results of this experiment show very clearly that the negative microscopic examination of stools as carried out in the routine post laboratory is not a trustworthy index of the absence of hookworms in the intestines. Thus we see from Table II that fifteen of the twenty-one cases negative to hookworm disease by the microscopic examination expelled some hookworms on treatment. The index of hookworm infection of the fazenda by the microscopic test works out as 63.7 per cent, whereas the true index of infection, if we count the four babies not treated as negatives, may be regarded as 85.5 per cent.

TABLE II.

Worm Counts in the 21 Cases Which Had Negative Microscopic Examinations.

Results.	Total No. of cases.	No. of cases with no worms.	No. of cases with worms.	Total No. of worms.	Average No. of worms per case.
Adults	11	2	9	165	18.3
Children	10	4	6	26	4.3
Adult controls	6	0	6	1,345	224.0

There were 4 adults negative to the microscope harboring 10 worms or more. Case 1, 33 yrs., harbored 98 worms; Case 2, 18 yrs., harbored 13 worms; Case 3, 35 yrs., harbored 21 worms; and Case 4, 20 yrs., harbored 12 worms. There was only one child, 7 years old, harboring 10 worms.

On the other hand, the individuals who were negative to the microscope had a low average hookworm count. Only one of the children negative to the microscope, and only four adults, harbored 10 worms or more. In fact, there is only one person on the fazenda, Case 1, who harbored 98 worms, to whom the microscope wrought great injustice. It is rather doubtful if the other three adults would have been compensated for the rigorous routine treatment with two doses of chenopodium, by the removal of their few hookworms—13, 21, and 12 worms respectively.

Another opportunity came later to give a test treatment and count the worms harbored by eleven cases that were negative to the routine post microscopic examinations in the Rezende laboratory in the State of Rio de Janeiro (Table III). The results were similar to those obtained in Experiment 1.

TABLE III.

Results of Cases with Negative Microscopic Stool Examination in Rezende.

	No. of cases.	No. of cases without hookworms.	No. of cases with hookworms.	Total No. of hookworms.	Average No. of hookworms per case.
Adults	8	2	6	29	4.8
Children	3	2	1	1	1

This method of study is a fair though severe test of the value of the routine microscopic examination in field work. A better cross-section of the results obtained by the microscope can be obtained,

however, if we allow the usual routine microscopic examination to be made of a large group of people and withhold the report. A typical group of these persons is then chosen, including various stations of life and all age groups, and the cases given a test treatment and the worms counted, without having the least idea as to the result of the microscopic examination. At the end of the experiment, worm count and microscopic examination results are compared. This method of approach was carried out upon six different groups of people and at three different hookworm posts. A summary of the results is given in Table IV.

TABLE IV.

Comparison of Results of Microscopic Examination of Stools with Actual Hookworm Count.

Laboratory.	No. of cases studied.	Cases positive by chenopodium.	Cases correctly diagnosed positive by microscope.	Worms per case.			Cases negative to microscope with 10 or more worms.	
				Positive to microscope.	Negative to microscope.			
					No. of cases.	Average No. of worms.	No. of cases.	No. of worms.
Bom Jardim.....	30	30	25	119	5	8.4	1	26
Santa Rosa.....	29	29	28	153	1	103.0	1	103
Magnolia (1).....	25	25	24	282	1	1	0	0
" (2).....	30	30	27	184	3	409	3	1 1 1
								1,157 34 36
" (3).....	26	26	26	254	0	0	0	0
Atibaia.....	20	20	19	206	1	10	1	10
Total.....	160	160	149		11		6	

Percentage of cases correctly diagnosed = 93 per cent.

Of the eleven cases incorrectly diagnosed by the microscope, five made no material difference, for they harbored less than 10 worms. Of the remaining six cases, there were four which harbored, 26, 34, 36, and 10 worms respectively in communities where the average worm infection was 150 to 200. There were two cases or about 1.2 per cent that were serious failures, one harboring 103 worms and the other 1,157 worms, and these can only be explained on the assumption that

the specimen tins became exchanged. The man with 1,157 worms for example was the father of an illiterate family of twelve children, all having very similar names, so that undoubtedly Joao senior exchanged specimen tins with one of the various Joao Juniors. Thus the error was probably not directly that of the microscope itself. Nevertheless, an important part of the microscopic technique is the proper collection of specimens, and any error in collection causes erroneous results in the microscopic report, and therefore the error must be charged to microscopic technique.

In summarizing the results of all these experiments we have a total of 192 cases examined by the routine microscopic method of the post laboratories with twenty-one errors. Nine of these errors were of very little consequence since each of these individuals harbored less than 10 worms.

THE MICROSCOPE AS AN INDEX OF CURE IN THE TREATMENT OF HOOKWORM DISEASE.

The microscope has had a more important function in routine field treatment work than the preliminary diagnosis of hookworm infection; namely, it has been used as a means to determine when an individual was cured, and the patients have been treated in some laboratories as many as ten times until the microscope gave a negative result. The fallacy of this method of treatment was clearly shown by the Malaya Board, and by our own results for last year for we now know that the first two routine treatments of the patient with chenopodium remove 97 per cent or more of all hookworms harbored, and the last six to eight treatments are a vain chase after a few refractory worms. We have also suspected that some of the cases that have been negative by the microscope after one or two routine treatments, were still harboring hookworms. An experiment was carried out to throw light on this point. The customary routine of field laboratories was followed out in this experiment.

Experiment 2.—Fazenda Santa Maria. 49 individuals were treated twice in the routine way by the nurse. 20 days after the last treatment all the cases were examined by the routine microscopic technique of the post laboratory, and we then treated all cases a third time with a test dose of chenopodium and counted the worms. The summary of the experiment given in Table V is interesting.

TABLE V.

Summary of Results of Experiment 2. Fazenda Santa Maria.

	No. of cases.	Average No. of worms per case.
Cases with negative microscopic examination yielding no worms ...	21	0
" " " " " " worms.....	12	5.5
" " positive " " " no worms....	2	0
" " " " " " worms.....	14	12.1

There were nine cases harboring 10 worms or more, two of which gave negative microscopic examinations. *There were twenty-one negative cases correctly diagnosed, and twelve incorrectly diagnosed.*

This experiment clearly shows that in a heavily infected hookworm district after two routine treatments of chenopodium, it is futile to attempt to determine by the microscope whether or not the last ultimate worm has been removed and the person cured. It gives one a much greater satisfaction to leave a community knowing that 97 per cent of the worms have been removed from the individuals of the community and to realize perfectly also that 3 per cent of the hookworms have been left, than to rest complacently in the false security that every case with a negative microscopic examination has *no worms* and to vainly waste time trying to remove the few worms remaining in those cases the microscope has chanced to find positive.

Another experiment (Santa Rosa) also shows the fallibility of the microscope in individuals who have been treated and who yet harbor a small remaining number of hookworms. In this case the preliminary treatment was not chenopodium but beta naphthol.

Experiment 3.—Santa Rosa. Twenty-nine cases were given the 18 gm. beta naphthol treatment of Bayma-Alvis for hookworm disease. 11 days after the last day of beta naphthol treatment all cases were given a routine microscopic examination; and the day following they were given a test treatment of chenopodium and their worms counted. The summary is given in Table VI.

TABLE VI.

Summary of Results of Experiment 3. Santa Rosa.

	No. of cases.	Average No. of hookworms per case.
Cases with negative microscopic examination yielding no worms...	6	0
" " " " " " worms.....	11	2
" " positive " " " no worms...	1	0
" " " " " " worms.....	11	17.5

In this experiment there were six negatives *correctly diagnosed* by the microscope and eleven *incorrectly diagnosed*, though the average number of worms per negative case is small.

The use of microscopic results as an index of the cure of hookworm disease after treatment is of little value and gives a false sense of security. Treated individuals still harboring from 5 to 20 worms may or may not give a positive microscopic examination as chance

dictates and much time and trouble is wasted in treating to a microscopic cure an individual harboring a half dozen worms whose eggs the microscope chanced to find, whereas there is a very good chance that the individual's brother may also still be harboring a half dozen worms, whose eggs the microscope *chanced not to find*.

DETERMINATION OF THE NUMBER OF HOOKWORMS REMAINING AFTER TWO ROUTINE TREATMENTS BY THE NURSE.

In the report of last year (2), we detailed the results of the treatment of 82 boys in a Reform School with two doses of chenopodium of 1½ cc. each with a 10 day interval. It will be remembered that the results were very satisfactory, for 97.1 per cent of their hookworms were removed by the treatment. This experiment was carried out under almost ideal conditions however, for discipline was excellent, and the routine of treatment was carried out with great precision. What we really desire to know is the result of treatment under field conditions by a hookworm post nurse who is giving routine treatments.

To determine this important point, four different experiments were carried out in three different posts and under conditions which subjected the efficiency of the post field treatment to a severe but fair test. The director of a given post was suddenly notified without previous warning that a worm count experiment was to be done in any zone where any nurse had recently completed a sufficient number of routine second treatments with chenopodium.

These people who had already received two routine treatments by the nurse were treated a third time with a large dose of chenopodium. All stools were saved in the usual way and all worms counted. A brief summary of the results obtained is given below.

Experiment 4.—Bairro Boa Vista. Ten persons in a very heavily infected community had been treated twice with chenopodium by the nurse. He had given the dosage each time in two equal doses at 6 and 8 a.m. without the use of a preliminary purge. The dose was the customary 1½ cc. with graded dosage for children. On our test treatment these ten cases yielded a total of only 134 worms, or 13.4 worms per case. There were no cures but five failures; *e.g.*, cases with 10 worms or more per case remaining. Two other cases in the same community illustrate the severity of infection of this district. They had received only one treatment of chenopodium by the nurse. These two cases still harbored an average of 168 worms per case.

Experiment 5.—City of Atibaia. The infection rate in this city was light and the average number of worms harbored in each infected case was correspondingly small. Ten individuals were treated in this city who had received two

routine treatments by the nurse. The drug had been given in divided dosage, 1½ cc. for adults, and without a preliminary purge. All cases were treated a third time with the full 3 cc. of chenopodium and their worms counted. They harbored a total of only 7 worms, or an average of 0.7 worm per case.

Experiment 6.—Rezende. This group was chosen because it had had an extremely heavy infection, with heavy *Ankylostoma duodenale* incidence. They were in such poor physical condition that the post physician had not felt justified in giving a full customary dose of 1½ cc. The dose given by the nurse was 1 to 1¼ cc. instead of the usual 1½ cc. and the treatment had been given in two equally divided doses without a preliminary purge. The results obtained by us on test treatment are summarized in Table VII. Five control cases that had had no previous treatment were treated at the same time and found to harbor an average of 472 hookworms each.

TABLE VII.

Summary of Results of Experiment 6. Rezende.

	Hemoglobin.	No. of cases.	Average No. of worms remaining after routine treatment with chenopodium.	Failures, with 10 or more worms remaining after routine treatment.
				per cent
Very heavily infected cases	15–39	6	131	66
Heavily infected cases	40–59	11	18.9	33
Moderately infected cases	60–85	11	3.4	0

Experiment 7.—Fazenda Santa Maria. This estate was chosen because it was typical of field conditions in São Paulo. It was a large coffee fazenda with the colonists under good discipline and with the owners giving hearty cooperation.

56 cases of all conditions, sexes, and various ages were treated a third time, having first been given two routine treatments by the nurse. The nurse had given the customary treatment of 1½ cc. divided into two doses without preliminary purge, repeating the treatment in 10 to 14 days, a graded dose being given to children. We gave the customary test treatment of 3 cc. of chenopodium and found an average residue of 5.8 worms per case. There were ten failures; *e.g.*, cases still harboring 10 worms or more per case. The highest worm count in any individual was 38 worms. Four control cases on the same fazenda that had had no previous treatment harbored an average of 176 worms per case.

These four experiments bring out certain important facts very clearly. In the first place they demonstrate that under good field conditions as in Fazenda Santa Maria, with cheerful cooperation and interest of the patients and with a moderately severe average infec-

tion, the results obtained in the routine treatment by the nurse approximate closely the results obtained under ideal experimental conditions. This can best be illustrated in a table of comparison (Table VIII).

TABLE VIII.

Two Treatments of 1½ Cc. of Chenopodium in Divided Dosage.

	Ideal experimental conditions. Pinheiro, 0.5 cc. 3 times, 1 hr. apart.	Field conditions, treated by nurses. Santa Maria, 0.75 cc twice, 2 hrs. apart. Experiment 7.
Cases treated	82	56
" cured	40	23
" cured, *per cent*	49	41
Total No. of hookworms removed, *per cent*	97.1	96.4 estimated.
Average No. of worms remaining per case after two treatments, *per cent*	3.7	5.8
Failures, 10 or more worms remaining per case, *per cent*	10.9	21.4

The results of this experiment were very gratifying, for they not only confirm the findings of our previous experiments, but also enable us to look forward to the future with confidence in the realization that the methods we have adopted as standard have withstood a severe test and proved entirely practical and satisfactory under usual conditions.

Experiment 4, Bairro Boa Vista and more particularly Rezende, show very clearly, however, that in districts which have a *very heavy* infection two routine treatments of 1½ cc. of chenopodium given by a nurse are not sufficient. It is very true that these cases were not all given the customary 1½ cc. of chenopodium, but even in those that were the results are unsatisfactory. The most satisfactory index seems to be to treat individuals in a very heavily infected community in relation to their hemoglobin. This is an especially satisfactory index in places where there are no other common conditions which produce severe anemia, as in malaria. For example, in Experiment 6 there were no failures in the treatment by the nurse in individuals who had a hemoglobin of 60 or over, whereas individuals with a hemoglobin of 40 or below still harbored an average of 131 worms after two treatments by the nurse.

There are zones where hookworm infection is very light, as in the city of Atibaia, which, by microscopic test had 25 per cent infected. Ten test individuals harbored only 0.7 worm per case after two routine treatments with chenopodium. It is more than probable that one treatment would have been sufficient in these cases, and it is doubtful if the inhabitants of zones with only 25 per cent infection really require any hookworm treatment.

Under usual conditions in Brazil, that is to say, with an average hemoglobin index of 60 per cent or more and an average infection of 50 to 200 hookworms per case, the routine field treatment of $1\frac{1}{2}$ cc. of oil of chenopodium in divided doses, given twice at 10 day intervals by a nurse, is an entirely satisfactory field method. In very heavily infected districts where the average worm count is 200 or more or where the hemoglobin of a non-malarial individual is below 60, we believe that two routine treatments of $1\frac{1}{2}$ cc. are not always sufficient to remove the hookworms, and a third is advisable. In lightly infected communities even two treatments are not necessary.

TREATMENT OF HOOKWORM DISEASE WITH LARGE DOSES OF BETA NAPHTHOL.

At the end of 1918, Gonzaga and Lima (3) of the São Paulo Sanitary Service described a method of field treatment of hookworm disease with beta naphthol, which had been most successful in their hands. The dose they employed was very large, but they claimed that no toxic symptoms were produced and that the treatment was a splendid one, since the drug was cheap, readily and inexpensively administered, almost as efficient as thymol, much more efficient than chenopodium, and with only one defect; namely, that it removed only hookworms and had slight effect on other intestinal worms. The criterion used in all their conclusions for the comparative experiments with thymol, chenopodium, beta naphthol, and other vermifuges, was the result of the microscopic examination of the stools, 12 to 14 days after treatment.

Their satisfactory results with the new method of beta naphthol administration were so striking that the treatment deserved a thorough trial, using as a criterion for comparison the more rigorous index of the worm count method.

To this end a series of experiments was undertaken on two different groups of people and in different locations. The method of beta naphthol treatment of Gonzaga and Lima was closely followed. No preliminary purge was given. On the first morning of treatment beta naphthol was given in hard gelatin capsules in the following dosage:

5 to 10 yrs.	3 gm.
10 " 15 "	4 "
15 " 20 "	5 "
20 " 50 "	6 "
50 yrs. and over	5 "

No children under 5 years were treated. The patients swallowed the capsules with as little coffee or other fluid as possible. They ate their meals at the regular hours but were on half diet, eating only rice, soups, macaroni, milk, and coffee, and omitting beans, coarse

vegetables, and heavy foods. The following morning the treatment was repeated and also the third morning—a total dose of 18 gm. of beta naphthol for adults with graded dosage for children. A purge of magnesium sulfate was given 2 hours after the administration of the beta naphthol capsules on the last day only, and the treatment was complete.

18 gm. seem an enormous overdose of beta naphthol, and we found that the bulk was so large that it was difficult to administer in capsules and impossible to administer any other way because of its acridity. Once swallowed, however, very little inconvenience was experienced, and the absence of vomiting, dizziness, headache, abdominal distress, prostration, etc., was in great contrast with the symptoms seen in similar groups treated with full doses of chenopodium. All stools of the patients were saved, washed, and the hookworms counted throughout the 3 days of treatment and also on the following day.

10 days following the beta naphthol treatment the patients were treated with the usual full test dose, 3 cc. of chenopodium, and the stools washed and the worms counted in the usual way to determine the number of hookworms that had been left by beta naphthol. The results of the two groups treated with beta naphthol were so similar that they are summarized together (Table IX, Column 1) and are compared with the results of routine chenopodium treatment (Table IX, Columns 2 and 3).

The results obtained with beta naphthol in this large dosage of 18 gm. were very good. In comparing them with the results obtained by us with chenopodium in Pinheiro, we find that there were fewer cures, a greater number of worms remaining per case, and a greater percentage of failures than in the chenopodium group, but this is excusable in that the rate of infection was considerably higher since the beta naphthol cases harbored an average of 186.3 worms whereas the Pinheiro cases harbored 132.7 worms per case. The most important index is the percentage of total hookworms removed and in this test the beta naphthol almost equaled chenopodium in efficiency. The results with beta naphthol under ideal conditions approximate very closely in every particular the results obtained with chenopodium under field conditions.

TABLE IX.

Comparison of Results in the Treatment of Hookworm Disease with Beta Naphthol with Similar Groups Treated with the Standard Chenopodium Method.

	6 gm. of beta naphthol on 3 successive days.	1½ cc. of chenopodium given twice with 10 day interval. Ideal condition. Pinheiro.	1½ cc. of chenopodium given twice with a 10 to 12 day interval. Field conditions and treatment given by nurse. Fazenda Santa Maria.
No. of cases treated	59	82	56
Total No. of hookworms removed	10,997	10,886	—
Average No. of hookworms per case	186.3	132.7	—
No. of cases harboring no more hookworms on test treatment.			
No. of cures	16	40	23
Cures, *per cent*	27.1	49	41
Cases negative to the microscope after trial treatment.			
Microscopic cures	17 of 29 examined.		32
Microscopic cures, *per cent*	58.5	—	66
Total No. of hookworms removed by trial treatment, *per cent*	96.4	97.1	96.4 estimated.
Average No. of worms remaining per case after trial treatment	6.7	3.7	5.8
Failures, cases with 10 or more worms remaining after trial treatment, *per cent*	22	10.9	21.4

There are other factors to be considered, however, in testing the usefulness of an anthelmintic besides its efficiency in the removal of hookworms. Among these are the cost of the drug, the ease and cheapness of the method of administration, discomfort and loss of time to the patient, efficiency in the removal of other intestinal worms, toxicity of the drug, etc.

Initial Cost of the Drug.—This is a factor of least importance, since the initial cost of the drug is a very small proportion of the total cost of the treatment. The difference in cost between 3 cc. of chenopodium and 18 gm. of beta naphthol, is not of sufficient importance to throw the balance very decidedly one way or another.

Cheapness and Ease of Administration of the Drug.—The routine treatment with chenopodium in the field requires that the nurse visit the family on 2 different days, at 10 day intervals. The beta naph-

thol treatment requires his attendance on 3 successive days. In thickly populated regions and readily accessible communities this additional visit is not a serious handicap, but in sparsely settled communities the additional cost of the beta naphthol treatment is considerable.

Ease of Administration.—1½ cc. of chenopodium is much more easily administered than 6 gm. of beta naphthol. Few people can swallow capsules of 1 gm., so that the routine dose of beta naphthol must be given in ½ gm. capsules, twelve of which must be swallowed. This is a long and often laborious process. Vomiting is frequent.

Discomfort and Loss of Time to the Patient.—Once the beta naphthol has been swallowed, the symptoms which result are few and short of duration. Some patients vomit and others complain of burning in the epigastrium, but after half an hour has passed all symptoms disappear and usually the individuals take up their usual daily duties. One group was treated in the busy harvest season and some patients worked in the fields throughout the 3 days of treatment. This is in contrast to chenopodium, for as a general rule 1½ cc. of chenopodium produce sufficient discomfort and weakness to incapacitate an individual for almost the entire day.

Efficiency in the Removal of Other Intestinal Worms.—There is no better remedy for the removal of *Ascarides* than chenopodium, whereas beta naphthol has very little effect upon them. Beta naphthol removed only 52 of 124 *Ascarides* or 41 per cent, whereas chenopodium removed 91 per cent or 454 *Ascarides*. Neither of the two vermifuges has great efficiency in the removal of *Tænia* and *Trichocephalus*. There is a great advantage, however, in using a vermifuge which removes a high percentage of *Ascaris*, particularly in a campaign that depends for its success upon its popular appeal. People will submit to the discomfort of a vermifuge if they get visible results, and *Ascaris* fulfills all requirements in this respect.

Up to this point, therefore, the advantages and disadvantages of beta naphthol and chenopodium more or less balance each other, though the balance may truthfully be said to incline in favor of chenopodium if the work is to be carried out in the field. There remains only the problem of the toxicity of the drug.

Toxicity of Beta Naphthol and Chenopodium.—Gonzaga and Lima state that 18 gm. of beta naphthol for adults with a graded dose for children produce no toxic symptoms, basing their conclusions upon 400 cases treated in the field. We have a much smaller series of cases, 79, but they were very carefully studied, twenty of them under hospital conditions, and our conclusions are at variance with theirs. We have found beta naphthol very toxic in certain cases. We have also been able to find many cases in the literature which substantiate our conclusions. The matter was of such great importance that it has been made the subject of a separate research (4).

The toxicity of chenopodium will be taken up separately. It suffices to say here that $1\frac{1}{2}$ cc. do not produce severe toxic symptoms in adults, but that the dose must be very carefully graded for children.

Considering all factors, therefore, we believe that the standard treatment of chenopodium, $1\frac{1}{2}$ cc. given twice at 10 day intervals, is much superior to 6 gm. of beta naphthol given on 3 successive days, in the field treatment of hookworm disease, because of the slightly greater efficiency in removal of hookworms, greater ease and cheapness of administration, greater efficiency in the removal of *Ascaris*, and the lesser danger of severe intoxication.

STUDIES OF THE BEST METHODS OF ADMINISTERING CHENOPODIUM.

There are certain open questions in regard to the best method of administering chenopodium in hookworm disease. Among these problems two were chosen for study: (1) The question as to whether a preliminary purge is a valuable part of chenopodium treatment; and (2) the question as to whether the dose of chenopodium should be divided in equal parts and given at intervals, or should be given all at one time. The following experiments were undertaken to give us some further information upon these subjects.

Value of Preliminary Purge in the Treatment of Hookworm Disease with Chenopodium.

Experiment 8.—Two groups of people as nearly comparable as possible were chosen for the first experiment. They lived in neighboring communities, performed the same tasks, ate the same kind of food, lived in the same kind of houses, etc. Each group was treated with chenopodium, 1½ cc. for adults with graded dosage for children. The drug was divided into two equal parts and the capsules given at 7 and 9 a.m. A final purge was given at 11 a.m. They were allowed a light supper on the day previous to treatment, but no breakfast. The only variant in the experiment was the preliminary purge. Group 1 was given a purge of 30 to 40 gm. of magnesium sulfate at 8 p.m. on the evening before treatment, whereas Group 2 received no preliminary purge. Stools were saved and worms counted in the usual way.

12 days after the trial treatment both groups received the usual test treatment of 3 cc. of chenopodium, the stools were saved, and the worms counted. A summary of this experiment is given in Table X.

The results of this experiment seem to show that the preliminary purge is of no value in chenopodium treatment when the drug is given in the customary routine way; namely, 1½ cc. divided into two equal doses, 2 hours apart, and followed in 1½ to 2 hours by a purge. In fact, better results were obtained by all standards of comparison except the percentage of cases cured when no preliminary purge was given.

TABLE X.

Comparison of Chenopodium Treatment with and without a Preliminary Purge.

	1½ cc. of chenopodium in divided dosage.	
	Group 1. With preliminary purge.	Group 2. No preliminary purge.
No. of cases treated	27*	28
Total No. of hookworms removed	2,996	4,152
Average No. of worms per case	110.9	148
Total No. of hookworms removed by trial treatment, *per cent*	75.0	83.0
Cases cured by trial treatment, *per cent*	29	14
Average No. of worms remaining per case after trial treatment	28.0	24.0
Failures, cases with 10 or more worms remaining after trial treatment, *per cent*	40.6	31

* There were originally 28 cases in this group but one case was so obviously an exception that it was removed from the summary. In this case 806 worms were removed on the test treatment—more than from all the other 27 cases together.

In order to carry the experiment somewhat further another community was chosen and an investigation planned in which the treatment by chenopodium was given in a different way from the previous experiment.

Experiment 9.—As in the previous experiment the group was divided into two equal and similar divisions of people that were living under identical conditions. They were given 2 cc. of chenopodium in a single dose in hard gelatin capsules at 7 a.m. At 9 a.m. they were given a saline purge. A light supper was allowed on the evening previous to treatment but no breakfast. All stools were saved and worm counts made in the usual way. The only variant was the preliminary purge. One Group, No. 3, was given a preliminary purge of 30 to 40 gm. of magnesium sulfate at 8 p.m. on the evening before treatment, while Group 4 received no preliminary purge. A summary of this experiment is given in Table XI.

The results of these comparative experiments are just the opposite from those obtained in Groups 1 and 2, for by every standard of comparison better results were obtained in Group 3 which was given a preliminary purge, than in Group 4, which received no preliminary purge.

These results are not contradictory however, for the dosage and the method of administration of chenopodium were different. In Groups 1 and 2 some, at least, of the chenopodium remained in the intestines for 4 hours, whereas in Groups 3 and 4 the drug remained only 2 hours in the intestines.

It is evident that in a chenopodium treatment where the drug remains only 2 hours in the intestines the preliminary purge prepared the intestines so that hookworm elimination is aided, whereas when we allow the chenopodium to remain in the intestines for 4 hours a

TABLE XI.

Results of Chenopodium Treatment with and without a Preliminary Purge.

	2 cc. of chenopodium in an undivided dose followed in 2 hrs. by a saline purge.	
	Group 3. With preliminary purge.	Group 4. No preliminary purge.
No. of cases treated	25	26
Total No. of hookworms removed	7,058	6,601
Average No. of worms per case	282.3	254
Total No. of hookworms removed by trial treatment, *per cent*	93.8	87.5
Cases cured by trial treatment, *per cent*	12	0
Average No. of worms remaining per case after trial treatment	17	31.5
Failures, cases with 10 or more worms remaining after trial treatment, *per cent*	36	65.3

sufficient time elapses for the drug to produce an effect upon the hookworms, whether or not the intestines have been prepared by a preliminary purge.

Conclusions.—When a treatment of chenopodium is given in a dosage of $1\frac{1}{2}$ cc. for adults, divided into two equal parts and administered 2 hours apart on a fasting stomach and followed in $1\frac{1}{2}$ hours by a purge there is nothing to be gained in giving a preliminary purge.

When a treatment of chenopodium is given in a single dose of 2 cc. for adults on a fasting stomach and followed in 2 hours by a purge, there is a distinct advantage in giving a preliminary purge.

Divided Dosage of Chenopodium with Preliminary Purge.

The question arose whether or not the chenopodium should be divided into equal parts or be given in a single dose. The data for this study are taken from three groups of individuals which were treated with chenopodium by three different methods for the elimination of hookworms. The groups were not exactly comparable in that they lived in different locations and under slightly different conditions, and the dosage of chenopodium was greater in one group than in the other two groups. The groups are identical in many features and conclusions may be drawn from the comparison if certain reservations are made. All three groups have the following features in common. They were all living in the country, eating the same kind of food, and belonging to the same race. The treatment was very similar. On the day before treatment, they were allowed a light supper and at 8 p.m. were given a preliminary purge. Chenopodium treatment was begun the following morning at 7 a.m. on a fasting stomach. After the chenopodium treatment, 2 hours after the last capsule, a purge of magnesium sulfate was given, and all stools saved and worms counted. The test treatment followed, in the customary way, 10 days later to determine the number of remaining worms. The only variants were the method of administering chenopodium and the size of the dosage.

Group 5.—Pinheiro. A group of young adults in an agricultural school. Chenopodium given in three doses of 0.5 cc. each 1 hour apart at 7, 8, and 9 a.m., a total of 1½ cc. (Table XII.)

Group 6.—Fazenda Itatiaia. A group of farm laborers. The chenopodium was given in two equal doses of 0.75 cc. at 7 and 9 a.m., a total of 1½ cc. for adults, with a graded dose for children. (Table XII.)

Group 7.—Fazenda Magnolia. A group of colonists on a coffee plantation. The chenopodium was given in a single dose at 7 a.m., 2 cc. for adults and 1 cc. to children 9 to 17 years, followed by a purge at 9 a.m. The criticism will at once arise that it is not fair to compare results obtained with different dosages of 1½ and 2 cc. when the point at issue is the question of division of dosage. The answer is that 2 cc. of chenopodium in a single dose and followed in 2 hours by a purge, when judged by the criterion at our disposal, namely the toxic manifestation of the drug on the patient, is not a greater dose than 1½ cc. divided in 2 parts and followed in 4 hours by a purge. That is to say, the toxic effects of chenopodium upon the patient are due to its absorption and when 2 cc. are

given in a single dose and followed in 2 hours by a purge, the symptoms of toxicity are less marked, than when a smaller dose, 1½ cc., is given and a longer time, 4 hours, allowed for absorption. (Table XII.)

TABLE XII.

Divided and Undivided Doses of Chenopodium with Preliminary Purge.

	Group 5. 0.5 cc. given 3 times.	Group 6. 0.75 cc. given twice.	Group 7. 2 cc. given at one time.
No. of cases	82	27	25
Total No. of hookworms removed	10,886	2,996	7,058
Average No. of hookworms per case	127.9	110.9	282
Total No. of hookworms removed by trial treatment, *per cent*	90.8	75	93.8
Cases cured by trial treatment, *per cent*	28	29	12
Average No. of worms remaining per case after trial treatment	12.1	28	17
Failures, cases harboring 10 or more worms after trial treatment, *per cent*	23.1	40.6	36

The results obtained in the undivided doses of 2 cc., Group 7, are better in almost every respect than in Group 6 where 0.75 cc. was given twice. In comparing Groups 5 and 7, the advantages of one balance the other. Thus Group 7 had a higher percentage of worms removed, but a low percentage of cures. This may be explained by the fact that the average infection in Group 7 was much heavier than in Group 5. Group 7 also showed a slightly greater number of hookworms remaining per person, and a greater number of failures, but Group 7 is entitled to a slight margin because of the higher index of infection. The most important comparison is the percentage of hookworms removed, and in this respect, Group 7 showed the most favorable results.

Conclusions.—Chenopodium in an undivided dose of 2 cc. for adults, and 1 cc. for children followed in 2 hours by a purge is just as effective or even more effective than 1½ cc. of chenopodium in divided dosage when the purge is given 4 hours after the first capsule of chenopodium. Furthermore, since the purge is given 2 hours sooner in the 2 cc. treatment there is less absorption of chenopodium, toxic symptoms are less marked, and there is less danger to the patient.

These conclusions apply only to cases in which a preliminary purge is given. In hospital, dispensary, or private practice the preliminary purge is nearly always practicable, but in a field treatment post, in widely scattered and thinly populated rural districts great difficulty is encountered in giving the preliminary purge.

A Study of Divided Dosage of Chenopodium without Preliminary Purge.

Two groups of individuals were studied in whom all factors were very similar. The variant was that one group was given a divided dose and the other a single dose. These two groups differed from the three preceding groups which we have just studied in that no preliminary purge was given.

Group 8.—Engenheiro Passos. A group of agricultural laborers and villagers. Chenopodium was given at 7 and 9 a.m. in two equal doses of 0.75 cc. each with graded dosage for children. The purge was given 2 hours after the last capsule of chenopodium.

Group 9.—Fazenda Magnolia. A group of colonists on a coffee plantation. The chenopodium was given in a single dose of 2 cc. at 7 a.m. with a graded dose of 1 cc. for children between 8 and 17 years. The chenopodium was followed by a purge at 9 a.m. No preliminary purge was given. The same criticism arises here that occurred in the preceding comparison; namely, that we are comparing two variants, division of dosage and variation of amount of the drug. From the point of view of field treatment, 2 cc. of chenopodium eliminated in 2 hours is not a greater dosage for the patient than 1½ cc. given in divided dosage and finally eliminated in 4 hours. (Table XIII.)

TABLE XIII.

Divided and Undivided Dose of Chenopodium Treatment without Preliminary Purge.

	Group 8. Divided dose of 0.75 cc. given twice at 7 and 9 a. m.	Group 9. Single dose of 2 cc. given at 7 a. m.
No. of cases	28	26
Total No. of hookworms removed	4,152	6,001
Average No. of hookworms per case	148	254
Hookworms removed by trial treatment, *per cent*	83.0	87.5
Cases cured by trial treatment, *per cent*	14	0
Average No. of worms remaining per case after trial treatment	24.0	31.5
Failures, cases harboring 10 or more worms after trial treatment, *per cent*	31	65.3

The results obtained in the comparison of these two groups balance each other more or less. In Group 9 a slightly greater percentage of worms was removed, but there was a greater number of worms remaining after treatment. There were no cures and a much greater percentage of failures. Group 9 is entitled to a slight margin, however, because of the higher index of infection.

The symptoms of toxicity were slightly less marked in Group 9 patients than in Group 8, and much less marked than in Groups 6 and 7. The reason for this difference is that the preliminary purge which was given in Groups 6 and 7 predisposes to absorption of the chenopodium.

Conclusions.—Though the results obtained in Groups 8 and 9 approximate each other very closely from all modes of approach, it is only fair to say that the advantage lies slightly with the divided dosage of 0.75 cc. of chenopodium given twice at 2 hour intervals, the last capsule to be followed in 1½ hours by a purge. These conclusions apply only when no preliminary purge is given.

General Conclusions as to the Preferable Method of Administering Chenopodium.

We mentioned before in the study of beta naphthol that there are other factors to be considered in the study of a method of hookworm treatment than the efficiency of the drug. It is true that efficiency is the most important consideration, but we must also consider the initial cost of the drug, ease and cheapness of administration, discomfort and loss of time to the patient, toxicity of the drug, etc.

If we are working under dispensary or hospital conditions, these foregoing experiments seem to show that the best method of administering chenopodium is as follows:

A preliminary saline purge at 8 p.m. of the day before treatment.

A single dose of 2 cc. of chenopodium for adults with graded dosage for children at 7 a.m. on the fasting stomach.

A saline purge at 9 a.m.

The method is slightly more efficient than the other methods employed, the drug is just as easily and cheaply administered, there is less discomfort to the patient, and less danger of toxic symptoms than

in the other methods, for the drug is quickly eliminated. The treatment may be repeated after 12 days.

Field conditions are very different from hospital conditions, however, and it is largely with field conditions that we are concerned. In a sparsely settled rural community, the administration of a preliminary purge is a difficult procedure to carry out and almost doubles the cost of administration. This factor alone is of sufficient weight to lead us to recommend a different method from the one recommended for hospital and dispensary practice as most suitable for field treatment, which is as follows:

No preliminary purge.

Chenopodium divided into two equal doses of 0.75 cc. each for adults given at 7 and 9 a.m. on a fasting stomach.

Finally a saline purge to be given at 10.30 a.m.

This method is slightly less efficient than the one recommended for hospital or ideal conditions, and produces about the same amount of discomfort, but it is much more easily and cheaply administered under field conditions. The method is also cheaper than the same dose divided into three parts and given hourly, for the 2 hour interval allows time for the nurse to treat a much larger number of persons on the same day. We realize that we may be criticized for sacrificing efficiency to cost, but the loss to patients treated in the field is not a serious one, since we recommend that two treatments should be given. If we estimate that the average rural Brazilian has 136.1 hookworms and imagine that this average individual is treated once by the hospital method and 93.8 per cent of his hookworms removed, he will still harbor 8.4 worms, whereas if he is treated once by the field method and 83 per cent of his hookworms removed he will still harbor 23.2 worms. If the second treatment removed only two-thirds of the remaining worms (a very moderate estimate from the results of our experiment in 1918) then the worms remaining in the individuals treated with the hospital method would be 2.8 and the individuals treated under field conditions would harbor 7.4 worms. Thus we see that the sacrifice of efficiency to cost was not great.

TOXICITY OF CHENOPODIUM.

There is little additional information to add to that already reported in the previous year and by other authors concerning the toxicity of chenopodium. We have had a good opportunity to observe its toxic effects, for we have given the maximum dose a great many times in the test treatment.

Certain it is that 3 cc. of chenopodium, given in three equally divided doses 1 hour apart on an empty stomach, and the last capsule followed in 2 hours by a purge, is a maximum adult dose. We never give the test treatment without making every preparation for sudden onset of severe toxic symptoms and collapse, and in case of signs of approaching toxemia, such as extreme dizziness, prostration, or stupor, the treatment is suspended, the saline purge given at once, and the results of this case are not included in the series. 3 cc. of chenopodium given in the above described manner, nearly always produces great discomfort and usually severe toxemia to the patients and should never be given as a routine dosage in the field. $1\frac{1}{2}$ cc. of chenopodium given in two divided doses 2 hours apart very rarely produces severe toxic symptoms in adults. Considerable discomfort with the well known characteristic symptoms is frequently observed but disappears as a rule very soon after the final purge has had effect.

It is our experience that children are much more susceptible to chenopodium than adults. We have treated almost no children under 8 years of age, and therefore can draw no conclusions in regard to very small children, but we know that the drug may be very toxic for children from 8 to 12 years. We have customarily given a test dose of $1\frac{1}{2}$ cc. of chenopodium to children between 8 and 14 years, and practically all the cases in which alarming symptoms have been produced in our studies have occurred in this age group. Fortunately, the children of this age usually respond readily to prompt treatment, with the result that we have had only one fatality in this age group.

We have had three fatalities during the year.

Case 5.—A weak old man, a drunken vagabond, and an inmate of the county hospital. He was obviously heavily infected with hookworm disease and the

attendant physician thought he might be made somewhat more comfortable if he received hookworm treatment. A small dose of chenopodium was given, 0.75 cc. He developed none of the common symptoms of chenopodium poisoning, but became weak from the purge. The following day he was found dead in his bed.

This instance was obviously one of bad judgment, and the case should not have been treated with chenopodium.

Case 6.—A young woman of 20 years, an inmate of a county hospital. She was subject to hysterical attacks but seemed normal otherwise. She had been given treatment by the post nurse with 1¼ cc. of chenopodium on Apr. 24, 1919, and 1½ cc. 10 days later. She had very few symptoms from these treatments. Our treatment, a test treatment of 3 cc. of chenopodium, was given 1 month after the last treatment by the nurse. Severe toxic symptoms did not develop until almost midday, but she responded to continuous vigorous palliative treatment and by night seemed well out of danger. The following day peculiar hysteria-like mental symptoms appeared, a late manifestation of chenopodium poisoning, which have been seen on two other occasions. She grew slowly and steadily worse and died at the end of a week.

This death is directly due to the administration of the large dose of 3 cc. of chenopodium and occurred despite constant vigilance and careful vigorous treatment. Where we erred in this case was not in the palliative measures applied after she received chenopodium. She should not have received the 3 cc. test treatment of chenopodium. Nevertheless, thirty others received 3 cc. of chenopodium in the same hospital on the same day, many of them being in much poorer physical condition than she was, and yet she alone suffered severe consequences. It is not known why she reacted as she did, while the others were not intoxicated. We have, in fact, very few criteria by which to judge whether a person will or will not react to a large dose of chenopodium. We can say definitely, however, that 3 cc. of chenopodium should not be given in divided doses in routine field hookworm work.

Case 7.—A child of 8 years. She had received a trial treatment of chenopodium 10 days previously. We planned to give her a test treatment of 1½ cc. of chenopodium, but as she became somewhat dizzy before the hour for the last capsule only a final ¼ cc. was given, a total dosage of 1¼ cc. Soon after the last capsule was swallowed she began to show signs of severe chenopodium poisoning, and rapidly exhibited all the characteristic symptoms, despite constant vigorous

palliative treatment. After a few hours she rallied and seemed out of danger, but 36 hours after treatment she began to go into coma, convulsions commenced, and she died about the 57th hour after treatment. This case can clearly be attributed to an overdose of chenopodium.

The problem of the best method and proper dosage in the treatment of children with chenopodium is not yet a settled one. Strong vigorous children certainly sometimes react very rapidly and alarmingly to the drug, and the maximum dose of $1\frac{1}{2}$ cc. for children of 8 to 12 years should never be given in routine field treatment.

GENERAL CONCLUSIONS AND SUMMARY.

1. The degree of hookworm infection in rural Brazil is very high, with an average of 136.1 worms per case in the various parts of Brazil that have been studied. These records include individuals from almost every state. Almost no individual over 8 years of age in rural Brazil is free from infection with hookworms.

2. The prevailing worm is *Necator americanus*, although *Ankylostoma duodenale* has been found in every district studied. The infection with *Ankylostoma* is very light but is increasing in places that have a changing population and much immigration.

3. The degree of infection varies directly with the proximity of the individual to the polluted soil.

Problems of General Interest in Relation to Improved Methods of Hookworm Treatment.

1. The value of the microscope in routine treatment of hookworm disease in the field is brought out. The microscope is of doubtful value in the preliminary diagnosis of hookworm disease. It does not yield an absolute index of the presence or absence of infection, but in special conditions it can be used to weed out those cases which have few hookworms. A few cases with heavy hookworm infection may be missed. The microscope is of little value as an index of cure. An individual in a heavily infected community (with an average of 200 worms each) who has received two routine treatments with chenopodium, still harbors an average of about six worms each. 60 per cent of the community is entirely freed from worms. Since it is a mere matter of chance whether or not the microscopic examination picks out an individual infected with six hookworms or even twice six hookworms, and since the presence of six worms is of no material importance to the individual, the futility of giving tertiary or quarternary treatments to these cases is apparent. The time and effort required could be expended to much better advantage in prophylaxis and educational propaganda.

2. Two routine chenopodium treatments by the hookworm post nurse in places of moderate or even heavy infection (average of 100 to 200 hookworms per case) is very efficacious, removing more than 95 per cent of the worms harbored. In very heavily infected areas, with an average of 250 hookworms or more per case, a third chenopodium treatment is advisable. Where infection is very light, two treatments, or even one are not urgently necessary.

3. Beta naphthol in 6 gm. doses given daily for 3 successive days is very efficient in the treatment of hookworm disease, removing 96.4 per cent of the harbored worms. Its routine use in the field is not recommended because it is less efficient than two treatments of $1\frac{1}{2}$ cc. of chenopodium in divided dosage, it is more difficult and expensive to administer, it does not remove *Ascaris* satisfactorily, and there is greater danger of serious intoxication.

4. The method of preference to be used in administering chenopodium will depend upon the conditions under which the work is to be carried out.

The Preliminary Purge.

The preliminary purge on the evening before treatment does not add to the efficiency of chenopodium treatment in routine field work, where chenopodium is given in a $1\frac{1}{2}$ cc. dose divided into two equal parts and administered 2 hours apart, followed in $1\frac{1}{2}$ to 2 hours by a final purge.

The Divided Dose.

A single dose of 2 cc. of chenopodium followed in 2 hours by a purge is more efficient and less toxic than $1\frac{1}{2}$ cc. divided into two equal doses, and given 2 hours apart, the last capsule to be followed in 2 hours by a purge. This conclusion applies only where a preliminary purge is given the evening before treatment.

When no preliminary purge is given, just the contrary occurs; that is, a 2 cc. dose of chenopodium given all at one time without a preliminary purge and followed in 2 hours by a purge is a less efficient method than when the method of dividing $1\frac{1}{2}$ cc. of chenopodium without the preliminary purge is used.

Five different combinations of chenopodium administration have been tested and all have been found quite satisfactory. They are tabulated below in the order of their relative efficiency.

Relative Efficiency of Chenopodium Administration.

Method 1. Undivided 2 cc. dose followed in 2 hours by a saline purge. A preliminary purge was used.

Method 2. 1½ cc. divided into three equal doses, and given 1 hour apart, the last capsule to be followed in 2 hours by a purge. A preliminary purge was given.

Method 3. 1½ cc. divided into two doses of 0.75 cc. and given 2 hours apart, the last to be followed in 2 hours by a purge. No preliminary purge was given.

Method 4. 2 cc. undivided dose followed in 2 hours by a purge. No preliminary purge was given.

Method 5. 1½ cc. divided into two doses of 0.75 cc. each and given 2 hours apart to be followed in 2 hours by a purge. A preliminary purge was given.

Since Method 1 is slightly more efficient than any of the others it would appear to be the method of preference, and can be applied under ideal hospital or dispensary conditions. It requires the administration of a preliminary purge which is an important item of additional expenses in field treatment. The same argument applies to Method 2. This method is even more difficult and expensive to administer than No. 1.

The method of choice for field treatment, therefore, is No. 3, for by this method a large number of worms can be removed with economy of time to the nurses.

The toxic symptoms produced by the five methods are about equal, though there are always slightly more toxic manifestations when a preliminary purge is given.

There is little to add concerning the toxicity of chenopodium except in regard to the maximum dose. 3 cc. of chenopodium are the maximum dose for adults and should never be given in routine field treatment; 1½ cc. are the maximum dose for children between 8 and 12 years and should never be given in routine field treatment.

SUGGESTIONS.

1. Since hookworm disease in Brazil is a rural disease, the greatest good can be done by limiting the work at first to heavily infected villages and agricultural regions instead of spending time in towns, cities, and industrial regions. Since the disease in Brazil appears to bear no relation to the type of soil, geographical location, race, source of water supply, kind of food, etc., but varies according to the proximity of the individual to the infected soil, special attention should be paid to workers of the soil.

We should think of the results of our work in terms of number of hookworms removed and not in terms of numbers of cases cured, for we have come to realize that we cannot expect to remove all the hookworms from the people of a community but can only remove a maximum number of hookworms at a minimum of expense.

It has been shown that more than 99 per cent of the population of rural Brazil over 6 years of age is infected with hookworm and therefore it would seem that a system of two treatments of $1\frac{1}{2}$ cc. of chenopodium to all individuals above this age could be applied here. As was mentioned in the résumé of the annual report for 1919 it should be possible in selected places to extend the scope of the hookworm campaign by means of social welfare and other like methods; also by taking advantage of native customs and local patriotic societies in the prosecution of the work.

The results of our work this year indicate that the Field Director must enlarge the scope of the survey, ascertaining by worm counts the regions of heavier infection so that he may exercise his judgment in the selection of localities for treatment.

One of the weaker points of the demonstration scheme at present is the nurse, or guarda. He cannot be depended upon in all cases to carry out faithfully the instructions of the post doctor, and the Field Director in laying out his work must count on a percentage of failures due to this cause.

2. The nurse of the post should give two routine treatments of chenopodium, using the method outlined below, at intervals of 10

to 12 days. The case should then be closed unless the patient (in a non-malarial region) has a hemoglobin of 60 per cent or less, when three treatments should be given. If the post nurse follows carefully the details of the routine treatment more than 95 per cent of the worms harbored will be expelled.

3. Beta naphthol in 18 gm. treatments should not be used in the routine treatment of hookworm disease. The post should limit its work at first to rural communities. Hemoglobin determination should be made. A preliminary microscopic examination of the stool need only be made in special instances. Most persons should receive two treatments of chenopodium 10 or 12 days apart. The treatment should be as follows:

A light supper but no preliminary purge. $1\frac{1}{2}$ cc. of chenopodium should be given the following morning in two equally divided doses 2 hours apart, on a fasting stomach followed in $1\frac{1}{2}$ to 2 hours by a saline purge of magnesium sulfate given with at least a glassful of water. When the bowels have acted well, the patient may breakfast. This treatment should be repeated in 10 days.

In non-malarial communities, if dealing with an individual who has a very low hemoglobin, 60 per cent or less, a third treatment may be given. More than three successive chenopodium treatments need never be administered.

If one is working under ideal conditions, as in a hospital or dispensary, the following more efficient method of chenopodium treatment for hookworm disease is to be recommended.

A preliminary saline purge, 30 gm. of magnesium sulfate with 300 cc. of water, is given the evening before treatment. The following morning 2 cc. of chenopodium is given at 7 a.m. on a fasting stomach followed by a final saline purge at 9 a.m. with a full glass of water. When the patient's bowels have acted well he may breakfast.

This last method of treatment is slightly more efficient and gives less discomfort than the previous one. It is not practical for field work because of the preliminary purge.

The dosage of chenopodium should never be measured by the drop method. We have experimented with various pipettes and have found that oil of chenopodium may vary between 18 and 70 drops to the cubic centimeter.

The technique of standardizing the number of drops per cubic centimeter for each new pipette is so simple that any field hookworm post technician can learn the method in half an hour. The dose should always be measured in terms of cubic centimeters, and until this method of measuring is adopted by the post laboratories, the dose of chenopodium given by them will be extremely variable and inaccurate.

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