PRELIMINARY REPORT ON CREOSOTE AS AN ADJUVANT IN LEPROSY TREATMENT [1]

By JOSE G. SAMSON and GABINO LIMKAKO

Of the Medical Section, Culion Leper Colony, Philippine Health Service

TWO TEXT FIGURES

INTRODUCTION

Points of similarity or resemblance between tuberculosis and leprosy make it seem reasonable that any feature of treatment useful in the former disease may prove of value in the latter. However, it is obvious that this would not necessarily be the case, though Muir [2] was led to express the converse opinion that the effective antileprosy treatments are among the best for tuberculosis. Therefore, before applying on a large scale to leprosy treatment any drug accepted as useful in tuberculosis, its value in the former disease should be established or at least clearly indicated.

Muir, after using Rogers's sodium gynocardate and sodium morrhuate in treating lepers, introduced a mixture of chaulmoogra ethyl ester, 1 milliliter; creosote, 1 milliliter; camphor, 1 gram; and olive oil, 2.5 milliliters, which he refers to as E. C. C. O. At the time the chaulmoogra ethyl esters were being tried in the Philippines in comparison with Rogers's and other preparations, as a result of which they were adopted as the best drug for routine treatment under existing conditions. At the same time (1921), the workers then at Culion tried, in a few cases of leprosy complicated with tuberculosis, a cod-liver oil modification of Muir's formula known here as M. C. C. O., with benefit, it seemed, to patients showing the primary infection. As it was a matter of considerable interest to determine definitely whether the addition of creosote to the routine ethyl ester preparation would give better results in treatment, we had become sufficiently interested in the matter to encourage us to carry

[1] Read before the Culion Medical Society, June 29, 1923. Published with the consent of the Director of Health and the approval of the Philippine Leprosy Research Board.

[2] Muir, E., Handbook on Leprosy. Cuttack, R. J. Grundy (1921) 63.

out a series of observations with this end in mind. The work done and the results obtained are set forth here.

TREATMENT GROUPS

For our purpose one hundred ninety-four patients of both sexes and of varying ages were selected. All had been treated for nearly a year, in different groups, all receiving for the last few months the plain (noniodized) chaulmoogra ethyl esters, and from all appearances they had improved to a greater or less extent as a result of the treatment.

The patients were divided into four main groups, an attempt being made to make these uniform so far as sex and age were concerned. The type and the duration of the disease and the extent of involvement of the tissues differed so widely that it was not considered advantageous to attempt to determine the groups on this basis. The cases were practically all of the cutaneous and mixed types, and moderately advanced, though on the average not to the point of being distinctly unfavorable for treatment. Each of us treated approximately one-half of each group, more or less independently.

The observation, at the time the data herein presented were obtained, had extended over a period of six months. Injections were given intramuscularly twice a week, except when for some reason or other injection was postponed.

The treatments used were as shown in Table 1.

TABLE 1.—*Treatments used.*

Group	Cases.	Treatment.
I	53	Chaulmoogra ethyl ester, intramuscularly.
II	49	C. E. E. intramuscularly, creosote by mouth.
III	43	C. E. E., creosote, and camphor mixture.
IV	49	C. E. E. and creosote mixture.

Group I, in which there was no change from the treatment previously given to all, served as the control. Group II was treated identically except that a pill containing 0.3 milliliter of creosote was given at each injection, totaling 0.6 milliliter of this drug per week when the patient took both treatments. The dose was made small in the desire to avoid gastric irritation. Group III was given injections of a solution with the formula chaulmoogra ethyl esters, 1,000 milliliters; creosote, 25 milliliters; camphor, 25 grams. The solution given Group IV differed from this in that no camphor was used and, after the first few injec-

tions, but 12.5 milliliters of creosote to 100 milliliters of the ethyl esters. The ordinary United States Pharmacopœia grade of creosote was used almost entirely on account of the cost of the beechwood variety.

DOSAGE

As all of the patients were accustomed to receiving injections of the plain ethyl esters, the dosage that it was found possible to give the different groups is a fair indicator of the irritation, local or distant, produced by each particular preparation.

In establishing the maximum tolerated dose the drug was pushed, being increased by 1 milliliter at a step to the point of production of untoward effects, either local or general; the next lower milliliter was taken as the amount tolerated by that patient. We have observed that on attempting subsequently to increase the dose beyond this point unfavorable effects were usually produced.

TABLE 2.—*Maximum tolerated dose of creosote.*

Group.	Cases.	Percentage receiving—				
		1 cc.	2 cc.	3 cc.	4 cc.	5 cc.
I	53	1.9	0	17.0	79.2	1.9
II	49	2.0	2.0	28.6	61.2	6.1
III	43	0	9.3	72.1	14.0	4.6
IV	49	2.0	4.1	63.3	30.6	0

The data given in Table 2 are plotted in fig. 1.

The similarity of the curves of Groups I and II, which received injections of plain esters, is striking, as is that of the curves of Groups III and IV, which received creosote-ester solutions. The difference between these two pairs of curves is of interest. From the dosage figures of Table 2 the following averages are obtained: Groups I and II, 3.8 and 3.7 milliliters, respectively; Groups III and IV, 3.1 and 3.2 milliliters.

Naturally, creosote taken by mouth in small doses (Group II) does not influence the total amount of the ethyl esters that can be given intramuscularly. On the other hand, it is apparent that the incorporation of creosote in the ethyl esters, at least in the concentrations used, does lessen the amount of the mixture that can be given without undesirable effects.

It is of interest that Group III could be given practically as large doses of the creosote-camphor solution (20 per cent of each) as could Group IV with approximately 11 per cent creo-

sote and no camphor. At the outset 20 per cent creosote without camphor was used in Group IV, but this was so irritating that the amount added to the 100 milliliters of ethyl esters was reduced to 10 cubic centimeters. The patients complained of pain during injection, and serious local inflammations developed subsequently. Therefore, it is clear that camphor in this combination does reduce irritation.

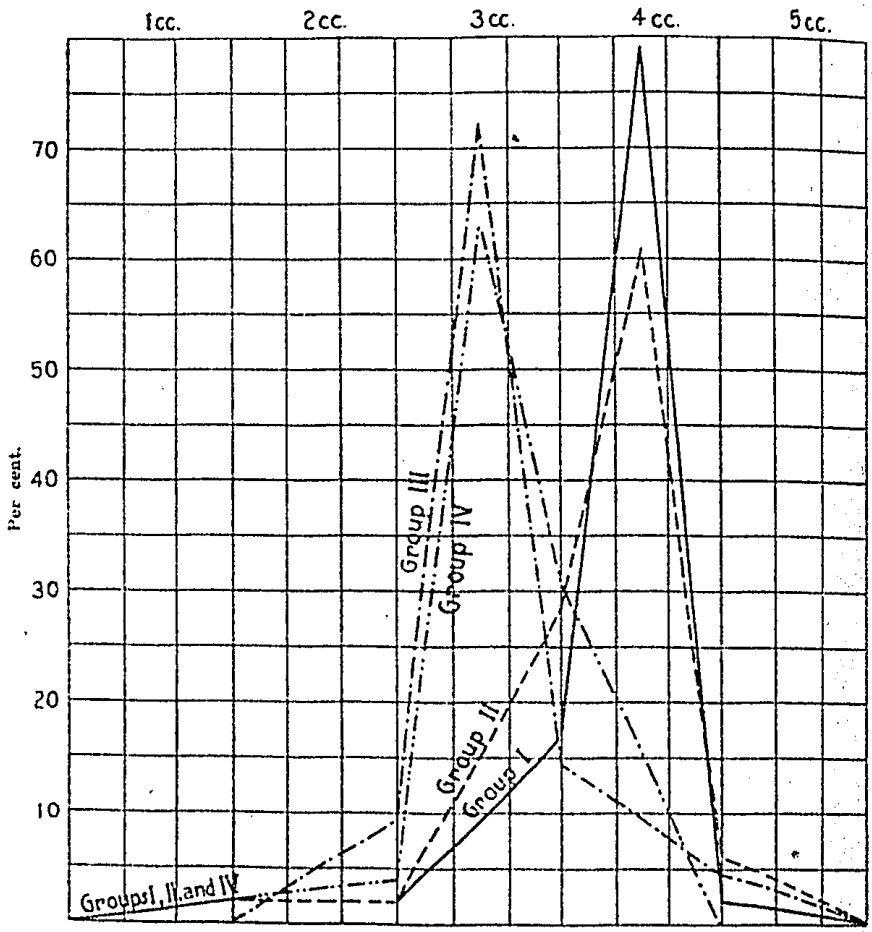

FIG. 1. The maximum tolerated dose of creosote in leprosy patients.

The matter of dosage is distinctly affected by the personal equation of the physician. For example, one of us reached a maximum dose of 4 milliliters in 91 per cent of his plain ethyl ester groups, the other in but 53 per cent. On the other hand, the first reached this dose in but one of his forty-seven cases receiving creosoted preparations (2.1 per cent), and the other in 49 per cent of forty-five patients.

INCIDENTAL EFFECTS DURING TREATMENT

In the course of the treatment various incidental conditions have arisen, resulting directly or indirectly from the treatment, that probably have more or less bearing on the results obtained.

LOCAL EFFECTS

The local effects of intramuscular injections of chaulmoogra ethyl esters are local inflammation and, infrequently, abscess formation at or near the site of injection. Local inflammation of moderate degree is a natural and constant reaction to this drug; however, usually it causes but little discomfort, lasts but a short time, and more or less completely subsides within a week. However, because of increase of dose, increased susceptibility or, perhaps, delayed absorption, more-severe reactions frequently occur which cause greater discomfort and last longer.

The number of such more-severe local reactions occurring in each group is shown in Table 3.

TABLE 3.—*Frequency of local reactions.*

Group.	Cases.	Injections.	Reactions.	Frequency per 100.	Cases reacting.	
					Number.	*Per cent.*
I	53	1,492	64	4.3	29	54.7
II	[a] 46	1,158	68	5.9	29	63.1
III	43	1,132	75	6.6	33	76.7
IV	49	1,209	102	8.4	36	73.5

[a] The reactions occurring in three hypersusceptible cases are not included here.

In Group I, 4.3 per cent of the injections caused acute cellulitis. In the total of 1,200 injections given Group II, local reactions were caused 101 times, or 8.4 per cent. Of these 33, or 32.6 per cent of the total number, occurred in three patients. These were abnormally susceptible to the ethyl esters, for they had very frequently exhibited this phenomenon while under the previous routine treatment. Excluding these unusual cases, the reaction percentage in this group is 5.9 per cent. Why there should have been more reactions in this group than in Group I is not apparent. The highest incidence occurred in Group IV, 8.4 per cent of all injections causing inflammation; in Group III, with twice as much creosote but with camphor added, the rate was considerably less.

With the plain esters (Groups I and II), local effects are manifested by moderate pain and swelling at the site of injections with more or less induration; the general well-being of the patient is seldom if ever affected. With the creosote solutions (Groups III and IV), the effects occur not only more frequently, but also with a greater degree of severity. The inflammation is more extensive, pain is more severe, and sometimes the temperature rises to as high as 37.9° C. Thus, though the incidence rates in Groups II and III are approximately the same, the reactions in the latter group were more severe. This is the chief reason why the average doses were not as large as those of the pure ester.

Chaulmoogra ethyl ester is itself a local irritant, but combined with creosote it appears that its irritating effects are distinctly increased. Camphor, somehow or other, seems very considerably to reduce irritation. The more irritating character of the creosoted drug is not a serious drawback for the reason that the susceptibility of patients to this irritation is more marked at the beginning of treatment; it tends to disappear, gradually but entirely, in the course of treatment, so that after a time it causes induration no more frequently than does the plain drug.

Abscess formation at the site of injection is an unusual occurrence. In the series of one of us (Samson) this has been observed once in Group I, four times in two patients in Group II, twice in each, and once in Group IV. All were examined bacteriologically and found to be sterile. The other of us (Limkako) has not had any abscess in this series.

CHOKING AND COUGHING

Choking is a phenomenon not infrequently observed a few minutes after injections of chaulmoogra derivatives. It is manifested by paroxysmal cough with flushing of the face, perspiration, at times dizziness, and slight irritation of the pharyngeal walls. Just how it is produced has not been absolutely proven, though it is held to be probably due to accidental rapid introduction of the drug into the circulation. In this connection, it may be remarked that patients with choking complain of creosote taste and creosote odor of the breath. While it may not be important, the relative frequency of this incident in the different groups of our series is of interest.

In Group I it occurred three times in three patients; in Group II, four times in four patients; in Group III, twelve times in eleven patients; and in Group IV, fifteen times in eleven patients;

one of the last group had it three times. There were, therefore, seven instances with plain esters and twenty-seven with the creosoted, occurring in 0.26 and in 1.2 per cent, respectively, of the total injections, a comparative ratio of nearly 1 to 5. This relative frequency with the creosoted preparations is in spite of the fact that the average dose used has been somewhat less than that of the plain drug.

SIMPLE FEVER

An unusual effect which was observed only at the beginning of the work, in patients receiving the creosoted preparations, was a quick, temporary rise of temperature. With noncreosoted ethyl esters slight rise of temperature is often found to occur and to persist for several days after an injection; indeed, slight hyperpyrexia, of less than one degree, seems fairly common in lepers; but the patients themselves are not aware of it.

From one to four hours after injection of the creosoted preparations the patients frequently complain of a sensation of heat, dizziness, and abundant perspiration. The face is flushed and the pulse slightly accelerated, the rate varying from 85 to 100 per minute, and the temperature increased. This has almost invariably been between 37.1° and 37.5° C., seldom reaching 37.8° C. This more severe reaction, as in the case of the local reaction, was seen only in the early stages of the work. After a number of injections, usually three to five, it no longer occurred.

LOCAL REACTIONS

Workers in India believe that, to get the best results, the administration of antileprosy drugs should be pushed until some degree of lepra reaction, that is, apparent activation of one or more of the lesions, with or without fever, is produced. This reaction, the mechanism of the production of which has never been explained to the satisfaction of all students of the disease, occurs universally in both the treated and the untreated lepers. It cannot be doubted that the chaulmoogra ethyl esters often serve to excite the lepra reaction. Table 4 shows the relative frequency of lepra reactions in the four groups of our series.

From Table 4 it is seen that, on the basis of total number of injections given, there was no greater incidence of lepra reactions in the creosote groups than in the plain. In fact, Group II gave the highest per cent, 3.3, while the others were almost identical, 2.5, 2.4, and 2.5. However, in the actual number of persons reacting there is a distinctly higher rate for Groups

III and IV, 49 per cent, than for I and II, 40 and 43 per cent, respectively.

TABLE 4.—*Occurrence of lepra reactions.*

Group.	Cases.	Injections.	Reactions.		Cases reacting.	
			Number.	*Per cent.*	*Number.*	*Per cent.*
I	53	1,492	36	2.5	21	40
II	49	1,200	40	3.3	21	43
III	43	1,132	27	2.4	21	49
IV	49	1,209	30	2.5	24	49

DOSE PRODUCING REACTIONS

These reactions were produced, as is to be seen in Table 5 by considerably smaller doses of the creosoted preparations than of the plain.

TABLE 5.—*Dose causing lepra reactions.*

Group.	Cases.	Doses.				Total.
		1 cc.	2 cc.	3 cc.	4 cc.	
I	53	----	11	15	10	36
II	49	3	7	19	11	40
III	43	6	9	10	2	27
IV	49	6	14	10	----	30

It has been our experience that the lepra reactions produced with the creosote solutions are not severe. For present purposes the classification of reactions used in this colony in 1922 will be employed here; namely, Type 1, exacerbation of old lesions with fever; Type 2, exacerbations of old lesions without fever; Type 3, eruption of fresh lesions with fever; and Type 4, fresh lesions without fever. The data on the types occurring are given in Table 6. For purposes of further comparison they are tabulated in Table 7, on the basis of duration, as follows: Very brief, less than one week; brief, one to two weeks; moderately long, two to four weeks; prolonged, more than four weeks.

TABLE 6.—*Kinds of reactions.*

Group.	Reactions.	Type 1.		Type 2.		Type 3.		Type 4.	
		Number.	*Per cent.*	*Number.*	*Per cent.*	*Number.*	*Per cent.*	*Number.*	*Per cent.*
I	36	4	11.0	5	14	5	14	22	65
II	40	3	7.5	4	10	7	18	26	65
III	27	----	----	1	4	4	15	22	81
IV	30	----	----	----	----	6	20	24	80

TABLE 7.—*Duration of reactions.*

Group.	Reactions.	Very brief.		Brief.		Moderately brief.		Prolonged.	
		Number.	*Per cent.*	*Number.*	*Per cent.*	*Number.*	*Per cent.*	*Number.*	*Per cent.*
I	36	16	44	14	39	2	5.5	4	11
II	40	12	30	21	52.5	4	10	3	7.5
III	27	7	26	13	48	3	11	4	15
IV	30	2	7	12	40	9	30	7	23

As regards the type of reaction, those in Groups I and II were essentially similar, with 65 per cent of Type 4; 14 and 18 per cent of Type 3, and less of the others. In Groups III and IV, Type 4 reactions predominated still more markedly, with 81 and 80 per cent, respectively. There was but one reaction of Type 2 and none of Type 1. In other words, practically no exacerbation of old lesions was produced by the creosoted esters, and but 15 and 20 per cent, respectively, had fever with the new lesions. The reactions caused by these preparations were milder than those produced by the plain preparations.

On the other hand, the duration of reaction with the plain preparations is very distinctly less than with the creosoted. However, in view of the mildness of the reactions, it is believed that this greater duration was not harmful. General statistics of the Culion work[3] indicate that, on the whole, the reactions of longer duration are harmful; the figures for improvement given below indicate that this was not the case in the present experiment.

RESULTS OF TREATMENT

The condition of the disease at the end of six months has been compared with that at the beginning of the present treatment, based on our records and the opinions of the patients and of ourselves. The findings are given in Table 8. Here all cases are classified as apparently negative, moderately improved, slightly improved, stationary, and worse.

The total improved, stationary, and worse are plotted in fig. 2.

According to these figures improvement under treatment with the creosoted preparations was distinctly greater than with the plain.

The totals (not shown in the table) were 51 per cent for the plain and 65 per cent for the creosoted. Comparing the four

[3] Personal communication from the acting chief physician; report in preparation for publication.

groups, Group I, with 43 per cent improved and 49 per cent stationary, gave by far the poorest results so far as improvement is concerned. The figures of Group II contrast interestingly, with 59 per cent improved and but 39 per cent stationary. The "worse" figure of this group, 2 per cent, is the lowest of the four.

TABLE 8.—*Progress under treatment.*

Group.	Cases.	Improved.			
		Negative.	Moderate.	Slight.	Total.
I	53	2	9	12	23
II	49	0	18	11	29
III	43	1	8	16	25
IV	49	1	15	19	35

Group.	Stationary.	Worse.	Percentages.		
			Improved.	Stationary.	Worse.
I	26	4	43	49	7.5
II	19	1	59	39	2
III	12	6	58	28	14
IV	12	2	71	25	4

With the creosoted preparations, Group III gave practically the same improvement rate as Group II, but the "worse" rate, 14 per cent, was by far the highest in the series, almost twice as high as Group I, and three and a half times that of Group IV. The latter group gave the most satisfactory figures of the series; the improvement rate, 81 per cent, is higher than the next best by 12, the stationary rate is the lowest, and the worse rate, 4 per cent, is comparatively low.

These are total figures, for the groups of both of us. The individual figures, arrived at independently, correspond fairly closely.

RELATION BETWEEN AMOUNT OF CREOSOTE AND IMPROVEMENT

It has been the experience in the treatment work at Culion that, in general, the total improvement rate goes hand in hand with the amount of chaulmoogra injected. In other words, the larger the dose regularly taken the better the improvement. As regards creosote, we cannot draw any definite conclusion as to the relation between the amount administered and the improvement on the basis of the present observations. However, the

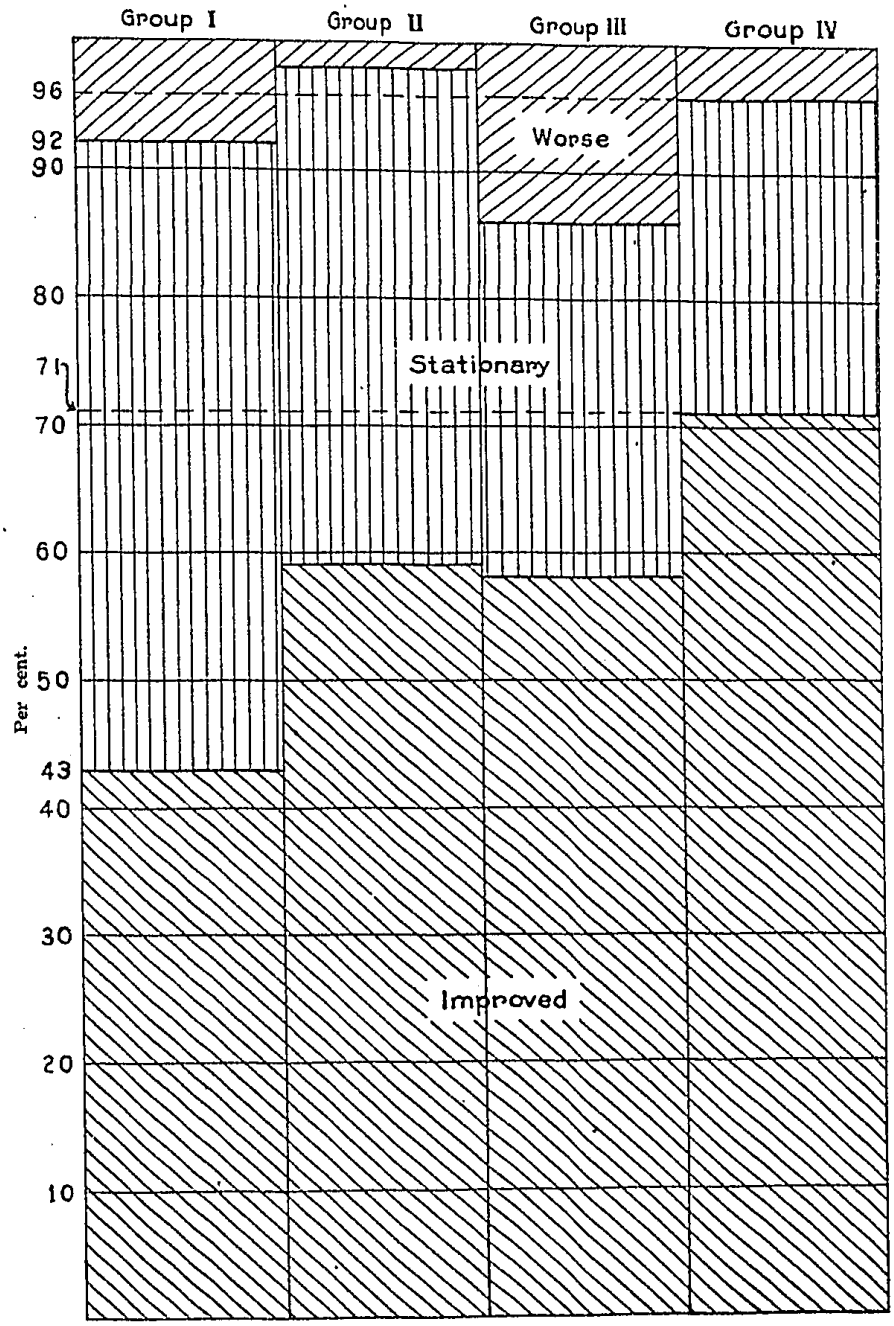

FIG. 2. Progress made by leprosy patients under treatment with creosote.

results obtained are of interest in this connection. In Group IV, the maximum amount per week would be 0.6 milliliter, or about 15 grams for the whole six months, in case there were no

absences. In Group III, with the 20 per cent solution in chaulmoogra ethyl ester, 0.6 milliliter of creosote was injected in each average dose of the mixture, 3 cubic centimeters, or at most 30 grams of creosote in the six months. In Group IV with which almost a 10 per cent solution was used, practically one-half of this total amount, 15 grams, would be given.

Here are seen two interesting contrasts; namely, between the same amount of creosote given by different routes and different amounts given by the same route. In Group II, 0.6 gram per week was given by mouth. The chief result, so far as was observed, was apparent stimulation of appetite, increase of weight, and generally improved condition, with at the end better figures for improvement than in the control group. In Group IV the same amount of creosote per week was given intramuscularly. The improvement, betterment of the general condition so noticeable in the second group, was not so marked, but the first figures on improvement of the disease are the best of the series, decidedly better than for Group II, in spite of the fact that the amount of chaulmoogra given was less.

In contrast with the last group is Group III, which received by the same route 1.2 milliliters of creosote per week, together with 1.2 grams of camphor. Here the improvement rate is practically the same as in Group II, and the worse rate is by far the highest of the series. Why this preparation should give poorer results than in Group IV is not clearly apparent. While there may possibly be an element of fortuity, this is believed not determinative. It seems improbable that a 0.6 gram dose of creosote given twice a week is excessive, even by the route used, though we know of no data on the intramuscular use of this drug. It has been suggested to us that the camphor, which is not a drug that one would naturally use in such a disease in considerable dosage over a long period, may be responsible for these less favorable results.

A sidelight on the results of the treatment is given by the effects on the weight of the patients. The changes that have occurred between September, 1922, and January 15, 1923, are shown in Table 9.

Most of the control group, Group I, gained weight, but Group II showed a higher percentage, 78 against 67. Those receiving creosote by injection gave lower percentages than either Group I or Group II. Group III, with the lowest improvement and highest worse rate, reflects these results in the weight changes.

TABLE 9.—*Percentages of patients who showed change in weight.*

Group.	Cases.	Increase.			
		Marked.	Moderate.	Slight.	Total.
I	53	11.3	36.8	18.8	66.9
II	49	10.2	36.8	30.6	77.6
III	43	2.3	18.6	25.6	46.5
IV	49	4.1	36.8	18.4	59.3

Group.	No change.	Decrease.			
		Marked.	Moderate.	Slight.	Total.
I	18.8	1.9	5.7	7.5	15.1
II	10.2	2.0	4.1	6.1	12.2
III	16.3	4.6	23.3	9.3	37.2
IV	24.5	4.1	4.1	8.2	16.4

CONCLUSIONS

From the results of the observations that have been made to date, given herein, the following tentative conclusions may be drawn:

1. Creosote given in small amounts by mouth to lepers serves to stimulate the appetite, resulting in increased weight and increase in the improvement rate in cases under chaulmoogra treatment.

2. Creosote introduced into the muscle causes marked local inflammation, which in some way is to some extent prevented or reduced by camphor.

3. A greater percentage of improvement has been secured with the admixture of a moderate amount of creosote in chaulmoogra ethyl ester.

4. Large amounts of creosote, with the addition of camphor to reduce irritation, give less beneficial results, perhaps because of the injurious effect of the camphor.

5. Creosote preparations apparently cause lepra reaction in a larger number of patients than do the plain preparations, but these reactions are not severe and apparently not harmful.

ACKNOWLEDGMENT

We wish to express our appreciation to Dr. H. W. Wade, acting chief physician of the Culion Leper Colony, at whose suggestion this work was undertaken, and who has assisted us in the analysis of the results and the preparation of this report.

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ILLUSTRATIONS

TEXT FIGURES