

1st May. Vomiting began after second dose so no more given.

3rd May to 30th May. Stool examined daily, no eggs seen.

2nd June. One *H. nana* egg seen.

3rd June to 2nd July. No eggs seen; discharged.

Case 9.—Male, *æt.* 42. Admitted for diabetes.

*H. nana* eggs found at routine stool examination.

Three courses of gentian violet were given, each consisted of 1 grain, *t.i.d.*, for three days with intervals of four days between them. There was no apparent effect on the infection which persisted throughout, and there was no nausea and vomiting so all the drug was retained. This seems to be an unusually resistant case.

Case 10.—Male, *æt.* 4. Admitted with 'dysentery' not confirmed by bacteriological or protozoological examination, and there is no evidence the symptoms were caused by *H. nana* because they cleared up before treatment was commenced.

*H. nana* and trichuris eggs found at routine stool examination.

7th to 9th September. Gentian violet  $\frac{1}{4}$  grain, *t.i.d.*

12th September. No *H. nana* eggs seen.

14th to 16th September. Gentian violet  $\frac{1}{4}$  grain, *t.i.d.*

17th to 21st September. No eggs seen.

21st to 23rd September. Gentian violet  $\frac{1}{4}$  grain, *t.i.d.*

22nd September. *H. nana* eggs again present.

No more eggs were seen up to the 1st October when patient was discharged. There was no vomiting throughout the treatment.

It will be seen that this case became negative after the first course of treatment, but it was decided to give two more courses of the same duration as in case 9. On the second day of the third course eggs again appeared which indicates the advisability of giving more than one three-day course even if the stool is negative after the first course.

Case 11.—Male, *æt.* 4. Admitted with 'dysentery' not confirmed by bacteriological or protozoological examination, and not caused by *H. nana* infection which was found at routine stool examination.

22nd to 24th December. Gentian violet  $\frac{1}{4}$  grain, *t.i.d.*

26th December to 4th January. No *H. nana* eggs seen.

5th January. Eggs and segments of *H. nana* found.

6th to 8th January. Gentian violet repeated.

9th to 19th January. No eggs seen.

20th January. Eggs again present.

21st to 23rd January. Gentian violet repeated.

Remained positive until discharged on 26th January.

This child never vomited so all the gentian violet given, was retained. The treatment varied slightly from that in case 10 because the second and third treatments were withheld until eggs appeared in the stools. This patient is still under observation.

Case 12.—Male, *æt.* 22. Admitted with *H. nana* infection but no symptoms. Gentian violet 1 grain, *t.i.d.*, for three days. No nausea or vomiting. Stool became negative three days after cessation of treatment and remained negative for three more days, after which the patient had to leave hospital. A stool brought for examination 17 days later contained *H. nana* eggs. This case is still under observation.

**Conclusion.**—These observations indicate that gentian violet is a valuable drug for treatment of *H. nana* infection, possibly the only one of any real value. Much more work is needed to decide whether a course of treatment for a week or longer or several courses of three days'

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## THE COMPARATIVE VALUE OF OIL OF CHENOPODIUM AND TETRACHLOR-ETHYLENE AS ANTHELMINTICS FOR USE IN MASS TREATMENT

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### Introduction

THE problem of hookworm infection bears several aspects of interest to the tea estate medical officer. From the clinical point of view of the practising physician, severe ankylostomiasis, though not an everyday occurrence, is a potent source of serious and, sometimes, fatal illness. 'Water-sore' or ground-itch, though not serious, is a very common disability which occurs during the summer months when the labour force is required to be at the peak of efficiency and when the physician is already busy dealing with the seasonal influx of cases of malaria and pneumonia. From the public health point of view of the medical officer, as

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duration at weekly intervals will prove to be the best. The interrupted form of treatment instead of a continuous course of six or seven days was tried on some of our cases in an effort to avoid the nausea and vomiting which is fairly common with this drug.

As far as our work goes the case records indicate that the minimum period of observation for a stool to be continuously negative is over 24 days, and hence is probably not far from the estimate based on the work of Shorb and Hunninen, quoted above. It is suggested that until further information on the subject is available this period should be placed at one month at least, but even a longer time than this is preferable until exact figures are obtained.

The results recorded are admittedly incomplete, and they are published with the hope that other workers, who have the opportunity, may be induced to follow the work up on the lines indicated in this paper.

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administrator, hookworm infection bears the cardinal stamp of interest in that it is eminently preventable by the provision of effective sanitation which prevents contamination of the soil and therefore removes the infective larvæ out of reach of the coolies' feet.

Unfortunately, very few tea estates have yet been provided with any system of sanitation at all so that the only way of breaking the circle of infection is by rendering worm-free the infected members of the population. Now, from this point of view, one hundred persons each harbouring one worm are of far more serious import than one person harbouring a hundred worms; for the area of scatter of infection is so much greater. In the tea districts of Assam, probably ninety per cent of the adult population harbour hookworms though the large majority of infections are very light so that, effectively to break the infectivity circle on its human side, virtually mass anthelmintic treatment is required.

The choice of anthelmintic is, therefore, a matter of some importance. For use in mass treatment, an anthelmintic must be:—

- (1) Non-toxic.
- (2) Reasonably palatable.
- (3) Easily dispensed.
- (4) Effective in one dose.
- (5) Inexpensive.

The fourth requirement is important as every treatment given means the loss to the estate of one day of labour, a vital consideration when production costs must be kept down to the minimum. Most authorities, *e.g.*, Chopra (1936), assess the value of an anthelmintic by comparing the proportion expelled of the estimated total worm load with the results obtained from some standard anthelmintic. We feel that this method is unsatisfactory. Since it must be based on experiments on heavily infected cases the results do not necessarily apply to the cases of light infection whose importance we have stressed. The heavily infected cases can always be dealt with individually since they are few in number. We consider that when assessing the value of a drug for mass treatment purposes, the only effective method is the determination of the percentage of infected persons, taken at random, who are rendered worm-free by one dose of the drug under test. Since it may be taken as accepted that the Clayton-Lane method of direct centrifugal flotation is the most accurate means of diagnosing hookworm infection, we feel that to find a stool egg-free when subjected to this test may be regarded as proof that the person who passed it is worm-free, provided a sufficient interval has elapsed since the exhibition of the anthelmintic.

The drugs in general use for expulsion of hookworms are carbon tetrachloride, oil of chenopodium, and tetrachlorethylene. Carbon tetrachloride is far from being non-toxic and several fatalities have been reported following

its use even when reasonable precautions have been taken. It is not, in our opinion, a suitable drug for mass treatment. Oil of chenopodium is probably, at present, the most largely used anthelmintic, but it is costly and is very unpleasant to take. There is a large literature in existence testifying to its efficacy and it is discussed in detail in all the standard textbooks of tropical medicine. Tetrachlorethylene, though it has been in use for at least ten years, has not amassed a considerable literature and a perusal of several standard textbooks provided only a limited amount of information. Manson-Bahr (1935) does not mention it at all, nor does Majumdar (1938). Banerjea and Bhattacharya (1938) mention it as 'a most effective anthelmintic against hookworm' and quote Maplestone for mode of administration. Chopra (1936), however, fully discusses its chemical constitution, pharmacological action and toxicity, and gives references to six papers on the subject. He comes to the conclusion that 'the cure rate with tetrachlorethylene is probably slightly greater than with (carbon) tetrachloride' and that 'tetrachlorethylene would be a very safe drug to employ as an anthelmintic'.

Manson (1934) carried out an extensive comparison between tetrachlorethylene alone, oil of chenopodium alone and a combination of the two and concluded that, within the scope of his investigation (which did not include examination by 'DCF') 'tetrachlorethylene is a safe and reliable anthelmintic for general use' and that 'tetrachlorethylene in a dose of 4 c.cm. and mixed treatment . . . proved to be definitely the best methods of treatment for mixed helminth infections and for hookworm infections'.

Maplestone and Mukerji (1937) have recently published a further series of cases confirming their previously recorded favourable impressions of tetrachlorethylene. They used the DCF method so that their figures are more comparable with ours. What information is available indicates that tetrachlorethylene is reasonably non-toxic and is effective. It is certainly more palatable than oil of chenopodium, is not more difficult to dispense, and its cost per dose is definitely less. The present investigation is an attempt to compare the efficacy of single doses of oil of chenopodium and of tetrachlorethylene in order to satisfy our fourth requirement, namely, efficacy in one dose.

#### *Material and technique*

The experimental subjects were 188 consecutive coolie patients admitted for hookworm treatment to estate hospitals under the senior author's charge. They had been picked out at labour force musters as being anæmic, or lethargic, or badly nourished, and in every case the existence of hookworm infection was confirmed microscopically by the senior author, personally, before treatment was given. Alternate batches of a dozen or so were treated with

the two drugs. Seventeen cases were given twenty minims of oil of chenopodium. Eighty-four cases had thirty minims of oil of chenopodium and eighty-seven cases had four cubic centimetres of tetrachlorethylene. Of these, ninety-four chenopodium cases (94 per cent) and forty-six tetrachlorethylene cases (52 per cent) were treated personally by the junior author. The remainder were treated substantially according to the same technique which was as follows :—

All the patients were treated as in-patients in order to allow of close observation and in every case the medicine concerned was poured directly into the mouth and the patient instructed to open the mouth afterwards to ensure that the whole dose had been swallowed. In any case where the medicine was vomited, the dose was repeated after a few minutes. The doses were administered in the early morning on an empty stomach and no food was given until noon when milk and sago were allowed. The oil of chenopodium used was guaranteed to be of *B.P.* strength and the tetrachlorethylene was obtained from a reliable source. The total dose of oil of chenopodium was split up into separate portions of ten minims each shaken up in one ounce of fifty per cent magnesium sulphate solution and the separate doses were administered at intervals of one hour. The total dose of tetrachlorethylene was given at one time shaken up with two ounces of a saturated solution of sodium sulphate. On the fourteenth day after administration of the anthelmintic a second stool was obtained from each case and subjected to Clayton-Lane's method of direct centrifugal flotation (DCF) by the senior author personally. The results were assessed as follows :—

No eggs in whole area of cover-slip = absolute cure.

One, two or three eggs in whole area of cover-slip = partial cure.

Four to twenty eggs in whole area of cover-slip = improvement.

More than twenty eggs was classified as 'no cure'.

Though, for the reasons stated above, we only attach importance to absolute cures we have included the other assessments in order to simplify comparison of our results with those of other workers.

TABLE

## OIL OF CHENOPODIUM (TWENTY MINIMS)

17 cases

Degree of cure	Number	Percentage
Absolute cure .. ..	<i>Nil</i>	..
Partial cure .. ..	1	5.9
Improved .. ..	<i>Nil</i>	..
Not cured .. ..	16	94.1

## OIL OF CHENOPODIUM (THIRTY MINIMS)

84 cases

Degree of cure	Number	Percentage
Absolute cure .. ..	4	4.8
Partial cure .. ..	7	8.3
Improved .. ..	19	22.6
Not cured .. ..	54	64.3

## TETRACHLORETHYLENE (FOUR CUBIC CENTIMETRES)

87 cases

Degree of cure	Number	Percentage
Absolute cure .. ..	42	48.3
Partial cure .. ..	23	26.4
Improved .. ..	9	10.4
Not cured .. ..	13	14.9

Table showing results of administration of single doses of anthelmintics.

## Results

The results of the investigation are shown in the accompanying table where we state the number of cases treated with each preparation, the number found in each class of 'cure' at the second examination and the same numbers expressed as percentages of those treated. It is obvious from this table that for efficiency in a single dose, tetrachlorethylene is infinitely superior to oil of chenopodium and, other things being equal, is the drug of choice for use in mass hookworm treatment. Our results with oil of chenopodium are, frankly, disappointing and are much inferior to those of other workers. Our standard of cure may have been more severe but another fact of possible importance is that some certainly, and possibly many, of these coolies have been previously treated with oil of chenopodium and it may be that a condition of 'chenopodium-resistance' can occur. We have never heard of such a condition being described but it seems an interesting possibility.

With regard to toxicity, all the patients treated with tetrachlorethylene experienced a sensation of drunkenness (which they rather enjoyed) lasting an hour or so. One case, a debilitated female of eighteen, suffered from severe vomiting, giddiness and marked drowsiness. After cold had been applied to the head she recovered and was perfectly well by the evening. Her cardiac condition was normal.

The coolies were emphatic in their opinion of the palatability of tetrachlorethylene as compared with oil of chenopodium. They considered it to have a sweet taste and a pleasant odour and pointed out that it did not cause any burning sensation in the mouth. These points all contrasted strongly with oil of chenopodium which is, by no means, one of their favourite drugs.

Tetrachlorethylene is simple to dispense using the method of administration described and has the added attraction to the compounder that he need only dispense one dose as against several.

Tetrachlorethylene is extremely cheap in use. One pound, costing Re. 1-14-0, represents twelve fluid ounces or approximately 360 c.cm. corresponding to ninety doses. The cost per dose is, therefore, one-third of an anna. One pound of oil of chenopodium, costing Rs. 13, represents nineteen fluid ounces, or 304 doses, the cost per dose being two-thirds of an anna—exactly double the cost of tetrachlorethylene.

#### Conclusion and Summary

(1) Attention is drawn to the importance in prophylaxis, as distinct from treatment, of mass anthelmintic treatment directed against the hookworms, and the properties of the ideal anthelmintic are stated.

(2) The assessment of the comparative value of anthelmintics is discussed and reasons given for preferring an assessment based on percentage of persons cured rather than percentage of worms expelled.

(3) Carbon tetrachloride, oil of chenopodium and tetrachlorethylene are discussed from the point of view of their literature.

(4) An experimental investigation into the efficacy of single doses of oil of chenopodium and tetrachlorethylene, checked by examination of the stools by Clayton-Lane's DCF method fourteen days after exhibition of the anthelmintic, is described and the results tabulated.

(5) It is concluded that tetrachlorethylene is a superior drug for mass treatment to oil of chenopodium as it more nearly fulfils all the five requirements of the ideal anthelmintic.

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We wish to record our appreciation of the kindness of Mr. F. O'Connor, Manager, Itakhooli T. E., in allowing us to fill his hospital with our cases and his unfailing courtesy in allowing them leave from their garden duties.

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## 'M. & B. 693' (2—SULPHANILYLAMINO-PYRIDINE) IN APE MALARIA

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In recent publications Chopra and Das Gupta (1938) and Das Gupta and Chopra (1938) have shown that certain sulphonamide compounds, namely soluseptasine and prontosil, have a definite action on *Plasmodium knowlesi* infection in rhesus monkeys, when administered in disproportionately large amounts as compared with human dosage. The reason for testing the activity of this new chemotherapeutic agent of the sulphonamide series on the same infection is to ascertain whether a relatively smaller dosage will prove effective in eradicating the infection. The daily dosage, as recommended for adults in various bacterial infections for which the drug is intended, is 4 to 8 tablets each containing 0.5 gramme of the compound. Considering the comparative weights of man and monkeys the dose for a monkey weighing 4 kilogrammes comes to 0.13 gramme. As previous experience has taught us that oral administration of drugs to monkeys is extremely difficult, we asked the manufacturers if they could make it suitable for parenteral administration. Accordingly they prepared an oily suspension of this compound, containing 0.5 gramme of the active ingredient in 2.5 c.cm.

*Experiment 1.*—Monkey (*Silenus rhesus*) weighing 4.184 kilogrammes was experimentally infected with *Plasmodium knowlesi*.

Date	Parasites per 1,000 leucocytes	Treatment	REMARKS
12-12-38	32,400	0.74 c.c. of the oily suspension = 0.15 gramme of the compound given intramuscularly.	
13-12-38	28,000	Do.	
14-12-38	4,200	Do.	
15-12-38	Very scanty.	Do.	Very scanty degenerating forms. Mononuclears with ingested hæmozoin pigment.
16-12-38	0	Do.	
17-12-38	0		

The blood was examined daily till the end of December 1938, thereafter once a week till the 24th February, 1939. No parasites have ever been found.