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ON THE EFFECTIVENESS OF CARBARSONE AS A REMEDY FOR AMOEBIASIS[1]

E. G. HAKANSSON[2]

From the Gorgas Memorial Laboratory, Panama, R. de P.

When carbarsone was added to the remedies for amoebiasis in 1931, the medical profession was depending mainly upon emetine hydrochloride, chiniofon, and acetarson in the treatment of this disease. Emetine hydrochloride was still the most effective and most widely used drug for combating the acute symptoms of amoebic dysentery, but had been found unreliable for permanent cures.

Chiniofon (Pulvis chiniofoni, U.S.P.), which under the name of yatren was first tried clinically by Mühlens and Menk in 1921 (1), had gained a widespread use and had been acclaimed by some writers as a more notable triumph for the treatment of amoebiasis than emetine in its day, but the records of well controlled results indicated a high percentage of failures to eradicate the disease. Acetarson, N.N.R. (Stovarsol) had been found to be an effective amoebicide but dangerously toxic in many cases. Numerous other drugs were used either as adjuvants to the above remedies or as the principal therapeutic agents. Ipecac and emetine bismuth iodide, in spite of their distressing emetic effect, were still employed. In India, Acton, Knowles, and Chopra (2, 3, 4, 5) were trying kurchi and its alkaloids. Bismuth subcarbonate, treparsol, arsphenamine, rivanol, and many other drugs had a

[1] Read before the Medical Association of the Isthmian Canal Zone at its meeting in May, 1937.

[2] Lieutenant Commander, Medical Corps, United States Navy. The writer is indebted to Mr. J. F. Buckner and Mr. H. A. Down of the Hospital Corps, United States Navy, for their able technical assistance, and to the members of the staff of Retiro Matias Hernandez for their generous assistance in the collection of specimens.

place in the methods of some clinicians. On the whole the therapy of amoebiasis was far from satisfactory.

Carbarsone as introduced by Reed, Anderson, David, Leake, and Johnstone (6, 7, 8) gave promise of a simplified and more effective therapy. The reports by these workers during the period 1932–1934 (9, 10, 11) indicated that in the so called carrier state of amoebiasis, carbarsone given orally would eradicate the infection in better than 90 per cent of the cases and that in the presence of dysentery almost equally good results could be obtained by administering the drug rectally as well as orally. In these therapeutic trials the average total dose was about 0.075 gram per kilogram of body weight which was given in divided doses over a period of ten days. If this treatment failed to clear the stools of *Entamoeba histolytica* the course was repeated at intervals of at least ten days. One of their patients received 0.204 gram per kilogram of body weight in six weeks (8) and another 2.1 grams per kilogram of body weight orally and rectally "over an extended period" (12).

Larger doses were recommended and used by other workers. Connor (13) states that at the Municipal Contagious Disease Hospital, Chicago, the dosage of carbarsone is "$\frac{1}{4}$ gram t.i.d. for ten days, which may be increased in some cases to $\frac{1}{2}$ gram t.i.d. without danger." The latter amount would be 0.213 gram per kilogram in the case of an adult weighing 70 kgm. (154 pounds). Anderson (14) reported that Dr. J. C. P. Fearington had employed a total oral dosage of 3 grams per kilogram over forty-eight weeks with no perceptible harm.

Very few toxic effects were being reported. Anderson and Reed (12) noted only one instance of carbarsone toxicity in 330 cases, "except for 7 cases having gastric distress with an early more toxic sample of the drug." Smithies, (15) however, reports four cases of severe toxic reactions including dermatitis of the exfoliative type, laryngeal and pulmonary edema, faulty vision due to papillitis and retinal edema, edema of ankles and wrist, and enlargement of liver and spleen; also, in several other patients nausea and vomiting and aggravation of diarrhea, and in one patient a slight icterus. With one exception these patients

had taken small amounts of carbarsone, only from 2 to 20 capsules (0.5 to 5 grams). Brown (16) states that two cases of toxic erythema and one case of neuritis have been reported to him. In 1936 Epstein (17) reported a death due to carbarsone poisoning. It occurred after the administration of only 5 grams, 0.083 gram per kilogram of body weight. The patient, a woman, 55 years of age, was in very poor physical condition and, as Epstein assumed, probably had a reduced tolerance to carbarsone.

REPORT OF OBSERVATIONS

In the early part of 1935 we began to treat some cases of amoebiasis with carbarsone. Having then in mind the tendency of physicians to increase the dose, it was decided to use the drug in larger doses than first recommended and to attempt to determine their effectiveness. Only oral administration of the drug was employed. A total of only forty-five cases were treated under controlled conditions; thirty-five of these were inmates of Retiro Matias Hernandez, an institution for the insane of the Republic of Panama, the remaining ten were laboratory technicians and members of their families living in Panama City.

Control of clinical trials

It was recognized that an attempt to estimate clinically the effectiveness of an amoebicide should meet at least the following four requirements:

1. The presence of an *E. histolytica* infection must be demonstrated beyond any possible doubt before beginning the treatment. In this no difficulty was encountered since we could collect any number of fecal samples in case of doubtful findings. Only unmistakable trophozoites of *E. histolytica* or the characteristic cysts were accepted as satisfactory evidence of infection. All identifications were made in both wet smears and wet-fixed stained preparations. It may be mentioned in this connection that most of our cases were heavily infected with other species of the intestinal protozoa. Only five had the single *E. histolytica* infection. Not less than twenty-four harbored four or more species of amoebae or flagellates. The effect of carbarsone upon

the various non-pathogenic species will not be discussed in this report.

2. The administration of the amoebicide must be supervised to insure that every dose of the prescribed amount is administered, and when the drug is given by mouth that it actually is swallowed and then not lost by regurgitation or vomiting. This requirement was strictly complied with in our work. The asylum inmates were even required to open their mouths to show that the capsules had been swallowed. No regurgitation or vomiting was observed in any case.

3. In order to make it possible to credit the therapeutic effect obtained to the amoebicide, it should be given without adjuvants and supportive treatment. Our patients received no adjuvant drugs of any kind and no supportive treatment such as special diet, and rest in bed. The asylum inmates had a diet which consisted mostly of rice, yucca, yam, plantain, bread, and meat. Even when having acute dysentery these patients would be up and about unless exhaustion compelled them to rest in bed. The patients among the laboratory personnel and their families, all of whom were carriers, continued their routine work and regular diet during the treatment.

4. After the termination of the treatment it should be determined whether or not the infection has been eradicated. This task has been troublesome to every one has attempted to ascertain the effectiveness of amoebicides, mainly on account of the difficulty of preventing reinfection and the lack of knowledge in regard to the length of time and number of examinations required after the treatment to prove that eradication has been accomplished. Among our patients satisfactory isolation to prevent reinfection was entirely impractical and no doubt the chances for reinfection were considerable, particularly among the asylum patients whose personal hygiene even under the careful supervision exercised at Retiro Matias Hernandez was largely beyond control. Our follow-up extended a year and comprised the examination of at least thirty-one fecal samples according to the following schedule: Three normally passed stools and one stool following catharsis during the first week after completion of the

treatment; one normally passed stool weekly during the following ten weeks, and in the twelfth week three normally passed stools and one following catharsis; then one normally passed stool monthly until the year had passed when again a series of three normally passed stools and one following catharsis were examined. In addition, stools after catharsis were obtained and examined whenever a scheduled single stool was formed and firm. In all instances a mild cathartic was administered in order to obtain a mushy stool rather than the usually unsatisfactory watery evacuation of purgation. If and when a patient became positive, three consecutive stools were examined for confirmation and then weekly or monthly stools for a record of his clinical condition. Stools were also examined daily during the administration of the carbarsone in order to determine the immediate effect of the drug. Each stool was examined in two to four wet smears and in wet-fixed preparations. The latter were stained with Heidenhain's iron-hematoxylin and searched for at least 30 minutes with a 2 mm. oil immersion objective and × 6 ocular. All wet smears were examined by the writer; the stained smears were examined by a technician with proved ability in the identification of intestinal protozoa, and by the writer when presenting doubtful findings. The normally passed stools, which with few exceptions had the formed consistency of cyst-bearing feces, were also concentrated for cysts. For this purpose the sugar flotation method described by Yorke and Adams (18) was used. Each concentrate was examined in two to four wet smears.

Comments on tabulated results

The forty-five cases that were treated under these controlled conditions have been arranged in five groups according to the dosage employed, and their condensed records tabulated (tables 1 to 5). The clinical conditions which are recorded as carrier ("Crr") and acute amoebic dysentery ("AAD") refer to the clinical phase which existed when the course of treatment was begun. Thus a patient who received more than one course may be listed as "AAD" for the first course and as "Crr" for a second, or vice versa. The carriers had grossly normal stools with cysts or

small inconspicuous trophozoites of *E. histolytica;* the cases of acute amoebic dysentery had the characteristic blood-and-mucus discharge with large vigorous *E. histolytica* trophozoites containing red blood cells. In no case was there any evidence of hepatic involvement or other metastatic complications.

In all cases the carbarsone was given in divided doses two or three times a day immediately after meals.

During the treatment and for a month thereafter the patients were observed for toxic effects, such as gastrointestinal irritation, dermatitis, jaundice, albuminuria, and impairment of vision. No ophthalmoscopic examinations were done and no tests for subclinical hepatic damage.

When evaluating the results as shown in the tables it should be recalled that negative signs for the first and twelfth week and for the twelfth month represent in each instance the findings in at least four stools (three normally passed and one after catharsis) and that not a few of the other negative signs represent more than the scheduled single examination. Further it must be kept in mind that no measures whatsoever to prevent reinfection were instituted and that therefore a positive stool may represent reinfection rather than recurrence.

Group A

Group A (table 1) comprises fifteen asylum inmates, nine males and six females, all adults in ages from 20 to 66 years.

Clinical condition. All were carriers. Case 46 had had an attack of acute amoebic dysentery six months before from which he had recovered clinically without treatment; the others had no history of dysentery.

Dosage. For this group the dose was 0.5 gram (2 capsules) daily for four weeks, exclusive of Sundays, a total of 12 grams. Note that due to variations in the weight of the patients the total amount of carbarsone per kilogram of body weight varied from 0.148 to 0.387 gram. The one and only toxic reaction observed occurred in this group; case 17, female, age 30, weight 39 kgm. (86 pounds), developed deep jaundice and glycosuria in the last week of treatment having then taken 10 of the 12 grams or 0.256

TABLE 1

Treatment of amoebiasis with carbarsone

Group A. Fifteen inmates of Retiro Matias Hernandez

Dose: 12 grams in four weeks, Sundays excluded, 0.500 gram daily

CASE NUMBER	SEX	AGE	CLINICAL CONDITION	TOTAL PER KGM. BODY WEIGHT	RESULTS AS OBSERVED DURING A FOLLOW-UP OF ONE YEAR																				
					1st 12 weeks after treatment												Subsequent 9 months								
					1	2	3	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12
				grm																					
422	M	34	Crr*	0.176	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
46	M	66	Crr	0.272	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
1092	F	35	Crr	0.342	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
184	F	35	Crr	0.154	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+
701	M	33	Crr	0.210	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr
157	F	46	Crr	0.260	−	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	Died	
572	M	20	Crr	0.387	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	Died
17	F	30	Crr	0.256‡	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+	+
560	M	39	Crr	0.176	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+	+
259	F	42	Crr	0.210	−	−	−	−	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+	+
404	M	44	Crr	0.210	−	−	−	+	Crr		+	+	2nd course, see table 4												
390	M	44	Crr	0.240	−	−	+	AAD†		+	+	+	2nd course, see table 4												
222	F	32	Crr	0.148	−	+	Crr		+	+	+	+	+	2nd course, see table 4												
385	M	30	Crr	0.167	+	Crr		+	+	2nd course, see table 4															
561	M	28	Crr	0.235	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

* Crr, carrier.

† AAD, Acute amoebic dysentery.

‡ Received only 10 grams on account of toxic effect.

gram per kilogram of body weight. The jaundice lasted about two weeks and the glycosuria six days. Except for the discontinuation of carbarsone no therapeutic measures were instituted. As far as could be determined the patient made a complete recovery.

Results. In all these carriers the stools were cleared of *E. histolytica* in two to three days. The number to be considered as cured will depend upon what criterion is accepted. If it is assumed that surviving *E. histolytica* could not have escaped detection in the eighteen examinations during the first twelve weeks then seven were cured, while with the standard of one year of follow-up only three were cured. About the twelve cases that became positive during the year it can be stated that some in all probability were reinfections but also that some certainly were recurrences. To assume that all were reinfections would imply a rate of 80 per cent per annum which is more than twice the incidence of *E. histolytica* among the inmates of this institution.[3] The early appearance of *E. histolytica* in some of these cases (in the first week in two cases) also points to recurrences. As a matter of clinical interest it may be noted that case 390 instead of persisting in the carrier state developed acute amoebic dysentery in the third week after treatment. This occurred incident to a maniacal episode and confinement and probably had no relationship to the carbarsone treatment. The two deaths in this group were due to intercurrent diseases, chronic cardiac disease in case 157 and bronchopneumonia in case 572.

Group B

Group B (table 2) includes seven asylum inmates, all adult males in ages from 33 to 49 years.

Clinical condition. Three were carriers; one of these (case 586) had had an attack of acute amoebic dysentery six months before this treatment, the others had no history of dysentery. Four

[3] In 1934 a survey of these inmates for intestinal protozoa, made by Doctor C. M. Johnson, protozoologist to the Gorgas Memorial Laboratory, showed an *E. histolytica* incidence of 35 per cent (45 per cent among the men and 25 per cent among the women).

TABLE 2

Treatment of amoebiasis with carbarsone

Group B. Seven inmates of Retiro Matias Hernandez

Dose: 6 grams in six days, followed by 12 grams in four weeks, Sundays excluded

CASE NUMBER	SEX	AGE	CLINICAL CONDITION	TOTAL PER KGM. BODY WEIGHT	RESULTS AS OBSERVED DURING A FOLLOW-UP OF ONE YEAR																				
					1st 12 weeks after treatment												Subsequent 9 months								
					1	2	3	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12
				grams																					
586	M	33	Crr*	0.460	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
474	M	34	Crr	0.486	−	−	−	−	+	Crr		+	+	+	+	+	+	Died							
406	M	44	Crr	0.383	+	Crr		+	+	2nd course, see table 4															
527	M	35	AAD†	0.304	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+
506	M	49	AAD	0.221	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+	+	+	AAD	+	+	
361	M	42	AAD	0.249	+	AAD		+	+	+	+	+	+	2nd course, see table 4												
589	M	33	AAD	0.300	+	AAD		+	+	+	+	+	+	2nd course, see table 4												

* Crr, Carrier.

† AAD, Acute amoebic dysentery.

had acute amoebic dysentery. One (case 527) had his first attack, the others had a history of several previous attacks during the preceeding two years. Case 361 was bedridden due to exhaustion, the others were able to be about and walk to the toilets.

Dosage. In this group, the four weeks' course of 12 grams was preceeded by a six days' course of 6 grams, 1 gram (4 capsules) daily. This increased the total amount per kilogram of body weight to an average of 0.343 gram with a variation from 0.221 to 0.486 gram. No toxic effects were noted.

Results. Only one of the three carriers remained negative for the year of follow-up. The early reappearance of *E. histolytica* (first and fifth week) in the other two suggests recurrences rather than reinfections. In the dysentery cases the blood and mucus and the *E. histolytica* disappeared in three to four days and the stools became mushy or formed showing no abnormality except a few degenerated pus cells and slight excess of mucus. In case 361, which was the most severe, small *E. histolytica* trophozoites reappeared in the stools with the institution of the smaller dose (0.5 gram, 2 capsules, daily) in the second week. By the fourth week the trophozoites were again large and contained red blood cells and in the fifth and last week of the treatment the patient was "glued to the pot" with the blood-and-mucus stool of acute amoebic dysentery. Case 589 also became positive while taking the smaller dose but clinical dysentery did not develop until the second week after the treatment. Case 506 remained negative until the eighth week after treatment and clinically cured for nine months and case 527 clinically cured throughout the year but with positive stools from the eighth week. The death of case 474 was due to bacillary dysentery.

Group C

Group C (table 3) deals with thirteen asylum inmates, eight males and five females, all adults in ages from 18 to 60 years.

Clinical condition. Twelve were carriers and only one of these (case 494) had a history of dysentery. The thirteenth case had acute amoebic dysentery, a primary attack of only two weeks' duration.

TABLE 3

Treatment of amoebiasis with carbarsone

Group C. Thirteen inmates of Retiro Matias Hernandez

Dose: 0.250 gram per kilogram of body weight in ten days

CASE NUMBER	SEX	AGE	CLINICAL CONDITION	TOTAL AMOUNT TAKEN	TOTAL PER KGM. BODY WEIGHT	RESULTS AS OBSERVED DURING A FOLLOW-UP OF ONE YEAR																		
						1st 12 weeks after treatment												Subsequent 9 months								
						1	2	3	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12
				grams	*gram*																					
287	F	40	Crr*	11.25	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
964	F	35	Crr	12.50	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
401	M	36	Crr	13.25	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
494	M	28	Crr	14.00	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
473	M	25	Crr	14.25	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
98	F	60	Crr	14.25	0.250	–	–	–	–	–	–	–	–	–	–	–	+	Crr		+	+	+	+	+	+	+
200	F	35	Crr	12.25	0.250	–	–	–	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+
252	F	40	Crr	12.75	0.250	–	–	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	Died	
442	M	25	Crr	15.75	0.250	–	–	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+
318	M	31	Crr	15.00	0.250	–	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+	+
387	M	45	Crr	16.00	0.250	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
409	M	35	Crr	14.25	0.250	–	–	–	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
1138	M	18	AAD†	12.75	0.250	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

* Crr, Carrier.

† AAD, Acute amoebic dysentery.

Dosage. For this group the duration of the treatment was shortened to ten days and instead of giving the same amount to each patient, the dose was varied with the weight of the patient. Having noted in the previous groups that more than 0.3 gram per kilogram of body weight in four weeks and more than 0.4 gram in five weeks could be taken without untoward effects, it was assumed that 0.25 gram per kilogram of body weight in ten days would be a safe dose. Since each capsule contains this very amount, this dose in practical terms is the same number of capsules as the number of kilograms of body weight. A person weighing 70 kgm. (154 pounds) would then receive 70 capsules (17.5 grams), seven per day. The largest person in this group weighed only 64 kgm. and the maximum total amount used was therefore 64 capsules (16 grams). No symptoms indicating toxic effects were observed.

Results. With this large daily dose of carbarsone the stools were clear of *E. histolytica* on the third day in all cases. The blood and mucus in the dysenteric case disappeared in two days and the stool passed in the morning of the third day of treatment was semiformed and normal except for some large degenerated pus cells. In this case and in four carriers the stools remained negative during the whole year of follow-up. In regard to the other eight cases it should be noted that not less than six became positive in the fourth to the seventh week after the treatment. Some of these must have been recurrences since it is improbable that six out of thirteen cases (44.5 per cent) would be reinfected within seven weeks. The death of case 200 in the eleventh month was due to bronchopneumonia.

Group D

Group D (table 4) includes the inmates who received more than one course. They have appeared in previous tables only to show their first treatment.

Dosage. The first course for all seven cases was one of small daily doses over a long period of time as taken by group A or B, the second course, and also the third in case 589, comprised the large dose of 0.25 gram per kilogram of body weight in the short

TABLE 4

Treatment of amoebiasis with carbarsone

Multiple courses

Group D. Seven inmates of Retiro Matias Hernandez

CASE NUMBER	AGE	SEX	CLINICAL CONDITION	TOTAL AMOUNT TAKEN	TOTAL PER KGM. BODY WEIGHT	DURATION OF TREATMENT	RESULTS AS OBSERVED DURING A FOLLOW-UP OF ONE YEAR																		
							1st 12 weeks after treatment												Subsequent 9 months						
							1	2	3	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12
				grams	*gram*	*days*																					
404	M	44	Crr*	12.00	0.210	28	−	−	−	+	Crr		+	+	2nd course												
			Crr	15.50	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−	−
222	F	32	Crr	12.00	0.148	28	−	+	Crr		+	+	+	+	+	2nd course											
			Crr	20.50	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+
385	M	30	Crr	12.00	0.167	28	+	Crr		+	+	2nd course															
			Crr	18.50	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+
406	M	44	Crr	18.00	0.383	35	+	Crr		+	+	2nd course															
			Crr	12.25	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+
361	M	42	AAD†	18.00	0.249	35	+	AAD		+	+	+	+	+	+	2nd course											
			AAD	17.50	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+
390	M	44	Crr	12.00	0.240	28	−	−	+	AAD		+	+	+	+	2nd course											
			AAD	12.00	0.250	10	−	−	−	−	−	+	Crr		+	+	+	+	+	+	+	+	+	+	+	+	+
589	M	33	AAD	18.00	0.300	35	+	AAD		+	+	+	+	+	+	2nd course											
			AAD	16.50	0.250	10	−	+	Crr		+	+	+	+	+	+	+	+	+	AAD		+	+	+	+	3rd course	
			AAD	16.50	0.250	10	−	−	−	−	−	−	−	−	−	−	−	−	+	Crr		+	+	+	+	+	+

* Crr, Carrier.

† AAD, Acute amoebic dysentery.

period of ten days as taken by group C. Note that this large per kilogram dose in case 222 called for a total of 20.5 grams, 82 capsules in ten days. No toxic effects were observed.

Results. Again it appears that carbarsone is more effective when given in large doses in a short period of time than when the daily dose is small and the treatment prolonged. This interpretation must be made with some reservations since at least in some of these cases the more favorable result of the short courses with larger daily doses may have been due in part to the preceeding course.

In case 404, the total amounts in the two courses were practically the same; when given in four weeks the stools were negative for only three weeks but when taken in ten days the stools remained negative throughout the year of follow-up. In case 406, both the total amount and the per kg. dose given in thirty-five days were significantly larger than in the short course and yet the long course was followed by positive stools in the first week while after the ten days' course the stools remained negative for three months. In case 390, the amounts of carbarsone were practically the same in the two courses; when given in twenty-eight days the patient not only became positive but developed acute amoebic dysentery in the third week after the treatment, but when given in ten days the stools were negative for five weeks and the patient clinically cured of the dysentery for the whole year. Case 361 offers a good illustration of the greater effectiveness of the drug when administered in a short period. It is the inmate whose stools became positive in the second week of the thirty-five days' course and who developed severe acute amoebic dysentery in the last week. No treatment was given until ten weeks later at which time he still had the dysentery. The short course then promptly relieved the dysentery and cleared the stools which remained negative into the fourth month. No relapse of dysentery occurred during the year of follow-up.

At the end of the year, one of the four carriers still remained cured. The three cases of dysentery were clinically cured but had positive stools. It is of interest to note that with a criterion of cure comprising a follow-up of only three months all but one

TABLE 5

Treatment of amoebiasis with carbarsone

Group E. Laboratory technicians and members of their families

Dose: Varied from 0.075 to 0.150 gram per kilogram of body weight in ten days

CASE NUMBER	SEX	AGE	CLINICAL CONDITION	TOTAL AMOUNT TAKEN	TOTAL PER KGM. BODY WEIGHT	RESULTS AS OBSERVED DURING A FOLLOW-UP OF ONE YEAR																		
						1st 12 weeks after treatment												Subsequent 9months						
						1	2	3	4	5	6	7	8	9	10	11	12	4	5	6	7	8	9	10	11	12
				grams	*gram*																					
1	M	34	Crr*	5.00	0.075	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
2	F	44	Crr	5.00	0.083	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
3	M	37	Crr	7.50	0.109	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
4	M	27	Crr	7.50	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
5	M	16	Crr	7.50	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
6	M	25	Crr	9.50	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
7	M	29	Crr	9.00	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
8	M	29	Crr	10.00	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
9	F	28	Crr	7.50	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
10	F	20	Crr	7.50	0.150	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–

* Crr, Carrier.

of these seven cases could be considered cured by the last course of carbarsone.

Group E

Group E (table 5) includes five laboratory technicians and five members of their families, all living in Panama City. Three were females and seven males; their ages varied from 16 to 44 years.

Clinical condition. All were carriers without history of dysentery or severe attacks of diarrhea; three had complaints referable to the gastrointestinal tract. In general they were in good physical condition.

Dosage. Case 1 and 2 received the minimum dose, 0.5 gm. (2 capsules) and case 3, 0.75 gm. (3 capsules) daily for ten days; the others were given 0.15 gram per kilogram of body weight in ten days. For a person weighing 70 kgm. (154 pounds) this dose is practically 1 gram (4 capsules) a day. No toxic effects were observed but case 9, female, complained of colicky pains in the epigastrium during the first day of the treatment. During the treatment they carried on with their work and as in the case of the asylum inmates, received no special diet or any other supportive treatment.

Results. All remained negative for *E. histolytica* during the year of follow-up.

SUMMARY AND COMMENTS

This report deals with the clinical effectiveness of carbarsone as an amoebicide when given orally in larger doses than usually recommended, and without any adjuvants or supportive treatment.

Two series of patients are reported upon. One comprises thirty-five inmates in an asylum for the insane to whom forty-three treatments were given, and the other ten members of laboratory personnel and their families each of whom received only one course.

In the former series there were six cases of acute amoebic dysentery and twenty-nine carriers, in the latter all were carriers. In no case were there any symptoms or signs of liver abscess or other lesions outside of the colon.

DOSAGE

In the forty-three courses given to the inmates three methods of dosage were employed: (1) 12 grams in four weeks, Sundays excluded, 0.5 gram daily in two doses. Fifteen adults, 20 to 66 years of age, received this course. The total amount per kilogram of body weight taken during the four weeks varied from 0.148 gram to 0.387 gram. (2) 6 grams in six days, 1 gram daily in three doses, followed by 12 grams in four weeks, Sundays excluded, 0.5 gram daily in two doses. Seven adults, 33 to 49 years of age, received this course. The total amount per kilogram of body weight taken during the five weeks varied from 0.221 gram to 0.486 gram. (3) 0.25 gram per kilogram of body weight in ten days. Twenty adults, 18 to 60 years of age, received this course, one of them twice. The total amount required for this dosage varied from 11.25 gram to 20.5 grams.

In the series of carriers from laboratory personnel smaller doses were used. Two received the minimum dose of 5 grams and one 7.5 grams in ten days, the other seven were given 0.15 gram per kilogram of body weight in 10 days.

The largest amounts administered per kilogram of body weight were as follows: 0.25 gram in ten days, 0.387 gram in four weeks, 0.486 gram in five weeks, and 0.630 gram in three months. The largest amount per diem was 2.25 grams (9 capsules) which was given for two days and followed by 2 grams (8 capsules) for eight days (Case 222, age 32, weight 82 kilograms).

TOXICITY

Only one patient showed untoward effects of the carbarsone. The symptoms, jaundice and glycosuria, developed after the ingestion of 0.5 gram daily for twenty days, a total of 10 grams, 0.256 gram per kilogram of body weight, and lasted about two weeks. The patient then made a complete recovery. One woman in the series of laboratory technicians complained of colicky pains in the epigastrium during the first day of treatment. It is quite possible that also some of the asylum inmates who were mentally deranged and indifferent to physical sensations may have suffered gastric or intestinal distress without revealing

these subjective symptoms. Considering the large doses administered, the fact that only a single case developed manifest signs of toxicity would seem to indicate that carbarsone taken by mouth is a remarkably safe arsenical.

EFFECTIVENESS OF CARBARSONE

In our attempt to estimate the clinical effectiveness of carbarsone in the various dosages, two developments particularly were observed, namely the immediate effect upon the *E. histolytica* and the dysenteric symptoms, and the length of time that the stools remained negative during a follow-up of one year. For these purposes the stools were examined daily during the treatment and after the treatment according to a schedule which comprised a thorough examination of at least thirty-one stools during the year.

The immediate effect. In the carriers even the small dose of 0.5 gram (2 capsules) daily, cleared the stools of *E. histolytica* in two to three days. No case of dysentery included in this report commenced treatment with this minimum dose but it was given for four weeks to four cases of acute amoebic dysentery (Group B) after the stools had been cleared of *E. histolytica* by larger doses. In two of these cases it failed to keep the stools negative, and in one of these it even allowed the return of the dysentery while the drug was being taken. A similar example of failure to clear the stools of *E. histolytica* with the daily dose of only 0.5 gram of carbarsone is recorded by Chopra and Sen (19).

The large daily dose of 0.25 gram per kilogram of body weight which was used in five instances of acute amoebic dysentery, was strikingly effective. The blood and mucus would disappear on the second or third day of treatment and the stools be of normal formed consistency and clear of *E. histolytica* on the fourth or fifth day. A few degenerated pus cells and tissue cells and occasionally lumps of thick gray mucus would persist for a few days longer. This rapid return to practically normal function of the colon appeared as magical as the well known effect of hypodermic injections of emetine hydrochloride.

Final results. Following twenty of the fifty-three treatments,

the stools were negative throughout the year of follow-up. One of these cases had acute amoebic dysentery, the others were carriers. One of the carriers received two courses, the others a single course. The dosage varied from 0.075 to 0.46 gram per kilogram of body weight taken in ten to thirty-five days, as shown in the tables.

If the negative findings of the follow-up in these cases be accepted as satisfactory evidence of eradication it can be stated that carbarsone given orally without adjuvants or supportive treatment has eradicated *E. histolytica* in twenty cases. It then also can be stated that carbarsone similarly eradicated *E. histolytica* in the thirty-two cases reported by Reed and Johnstone (11) who followed their patients for 13½ to 22 months after treatment, examining three stools on consecutive days at intervals of two to four weeks. This record of 52 cases remaining negative for a year or more after treatment by a single drug is unique in the literature on the therapy of amoebiasis. There are many reports of series of cures effected by the use of the many amoebicides which have been tried and are being tried and many cases have been recorded as having remained cured for a year or longer but few indeed of these cures, according to the published records, have been verified by sufficient examinations of fecal samples.

Following thirty-three of the fifty-three treatments the stools became positive during the year of follow-up. In view of the fact that no measures for preventing reinfection were instituted it is highly probable that in not a few instances these positive findings represented new infections rather than recurrences. In fact, noting that no case in group E (laboratory technicians and members of their families) became positive during the follow-up and knowing that the chances of reinfection in this group were much less than among the asylum inmates one may suspect that most of the positive findings were due to reinfections. This would apply particularly to the carriers in group C, all of whom received a considerably larger dose than cases in group E. However, as noted in the discussion of the various groups, the post-therapy findings point convincingly to some recurrences in each group of asylum inmates, recurrences after the four and five

weeks' courses with small daily doses, as well as after the ten days' course with the large daily dose.

Relative effectiveness of the various forms of dosage. Out of the rather confusing data bearing on this point the following findings of significance may be noted. In recording these the assumption is made that an actual eradication of *E. histolytica*, and thus a cure, had been effected in the patients whose stools were negative throughout the year of follow-up.

1. A small daily dose of 0.0075 gram per kilogram of body weight (approximately 0.25 gram, one capsule, twice daily for an average adult) given for ten days will cure some carriers.

2. In other carriers this dose will fail to cure even though continued over a period of four weeks.

3. Even a large daily dose of 0.025 gram per kilogram of body weight (1.75 gram, 7 capsules, daily for an adult weighing 70 kgm.) given for ten days may fail to cure some carriers.

4. In the presence of acute amoebic dysentery the small daily dose of 0.0075 gram per kilogram may not only fail to cure, but may even be insufficient to clear the stools of *E. histolytica* and to control the dysentery.

5. The large dose of 0.025 gram per kilogram promptly relieves the dysentery and brings about a clinical cure and in some cases eradication of the infection and actual cure.

No conclusions can be drawn in regard to the percentage of cures effected by the various forms of dosage, mainly on account of the small number of cases in each group and the probable occurrence of reinfections. However, as noted in the discussions of the various groups, the immediate effects on the *E. histolytica* in the stools and the clinical results indicate definitely a greater effectiveness of large doses for ten days than small doses for four or five weeks.

FACTORS OTHER THAN THE AMOEBICIDE INFLUENCING THE THERAPEUTIC RESULTS

Although our patients received no form of treatment except the carbarsone it seems likely that other factors were involved in the therapeutic effects.

1. The extent of the amoebic lesions undoubtedly is of the greatest importance. Note, for example, that in group E, two carriers were cured with the small dose of 0.5 gram daily for ten days while the same dose in a case of acute amoebic dysentery (case 361, group B) allowed a recurrence of blood-and-mucus stools and trophozoites with red blood cells even while the drug was being taken; further, a case of acute amoebic dysentery (case 1138, group C) of only two weeks' duration and in all probability with relatively superficial lesions was cured clinically and protozoologically by 0.25 gram per kilogram of body weight given in ten days, but in four instances of acute amoebic dysentery with histories of previous attacks for at least two years the same dose

TABLE 6

Effect of carbarsone on large and small races of E. histolytica

	BEFORE TREATMENT	AFTER TREATMENT			
		Large races, more than 10 microns		Small races, 10 microns or less	
		Eradication	Recurrence	Eradication	Recurrence
Large races only	13	4	9		
Small races only	9			2	7
Both large and small races	14	7	7	3	11
Totals		11	16	5	18

effected merely a clinical cure which in one instance lasted only four months.

2. Large and small races of *E. histolytica* may vary in resistance to carbarsone. The examination of the asylum inmates before and after the treatments included measurements of *E. histolytica* cysts in order to determine the races present in each case. The races were determined in all but seven inmates who passed only trophozoite-bearing stools before the treatments. The findings are shown in table 6. Note that 11 of the 27 large race infections, 40.7 per cent, were eradicated, but only 5 of the 23 small race infections, 21.7 per cent. The fact that some of the "recurrences" in all probability were reinfections, as previously pointed

out, does not seem to be significant in this connection since the number of large and small races, and presumably the chances of reinfection, were almost the same, 27 and 23 respectively. It would seem then that the smaller races may have a higher resistance to carbarsone. One gains this impression particularly when noting the results in the 14 cases with both large and small races. In these instances the exposure to carbarsone must have been practically the same for all races and yet four small races survived when large races were eradicated.

3. The better food and better physical condition of the laboratory personnel and their families may explain to some extent the uniformly good results in group E.

4. Constipation may possibly interfere with the amoebicidal action of carbarsone by preventing diffusion of the drug in the contents of the colon and free contact with the mucus membrane. One of the carriers in group A, case 561, who became positive in the first week after treatment may have been an example of this condition; he was severely constipated passing only hard dry stools.

CRITERION OF CURE

With a view of finding a practical criterion of cure a special attempt was made to determine during the first week following the treatment whether or not an eradication of *E. histolytica* had been effected. The data on the follow-up indicate that this cannot always be done, which confirms similar observations by Walker and Sellards (20), Willets (21), Dobell (22), Craig (23, 24), and other workers. *E. Histolytica* was found during the first week in only five of the thirty-three cases whose stools became positive during the year of follow-up. In two of these instances the stools had been positive during the last part of the treatment leaving then only three recurrences detected in the first week. Our findings also indicate that *E. histolytica* when surviving a treatment probably can escape detection in fecal samples four to five weeks. Definite conclusions on this point

cannot be made on account of the probability of reinfections and insufficient fecal samples subsequent to the first week. More information on the chances of finding *E. histolytica* at various intervals after treatment is required before a definite criterion of cure can be established.

SUGGESTIONS IN REGARD TO THE USE OF CARBARSONE

The experience with carbarsone above recorded obviously is insufficient for any definite recommendations as to changes in the method of its administration. However, the findings seem to point to the following tentative suggestions:

1. The amount of carbarsone to be used should be given in divided doses after meals over a period of not more than ten days, as recommended by Reed and his co-workers.

2. The dose should be varied according to the clinical condition of the patients: (*a*) For carriers, a total dose of 0.075 gram per kilogram of body weight in ten days (approximately 0.5 gram, two capsules, daily for an adult weighing 70 kgm.) may suffice but twice as much, 0.15 gram per kilogram of body weight in ten days (approximately 1 gram, four capsules, daily for an adult weighing 70 kgm.) may prove to be necessary for some carriers. (*b*) For cases of amoebic dysentery a total dose of 0.25 gram per kilogram of body weight in ten days (1.75 gram, seven capsules, daily for an adult weighing 70 kgm.) may be necessary although the justification for such a large dose may be questioned until more evidence of its harmlessness is obtained.

3. When a first course of carbarsone fails, a second course may cure. To forestall renewed invasion of the colon by the parasite it should be commenced as soon as *E. histolytica* reappears in the stool, provided that an interval of at least ten days has elapsed to prevent cumulative toxic effects from the first course.

In connection with these suggestions it should be kept in mind that carbarsone is only one of several valuable remedies for amoebiasis. Many workers have found that a judicious combination of two or more remedies have succeeded when one has failed.

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