

TREATMENT OF CHRONIC INTESTINAL AMOEBIASIS WITH CARBARSONE

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THE difficulty of curing chronic amoebiasis is well known to physicians practising in the tropics. An acute attack of amoebic dysentery can in the majority of cases be successfully relieved by proper treatment, but eradication of the chronic intestinal infection with *Entamoeba histolytica* is a difficult matter. A large number of remedies are supposed to cure this condition, but most of these reduce the infection to a low level, so that the patient's own natural powers of resistance can keep in check the parasites which still remain in the body. Many of these patients become carriers.

Of the drugs used against amoebiasis emetine, although it is an excellent drug in acute amoebic colitis, often fails to cure the chronic condition. Halogenated oxyquinoline derivatives, such as yatren (loretin, quinoxyl), chiniofon, vioform, etc., were highly spoken of but have proved disappointing. Some dye derivatives such as Rivanol (2-ethoxy-6:9 diamino acridine) and bismuth subnitrate have been tried with no better results. Acton and Chopra (1931 and 1932) tried the bismuthous iodide compound of the total alkaloids of *Holarrhena antidysenterica* in doses of 10 grains twice a day by the mouth for 10 to 20 consecutive days and they cured 73 per cent in a series of 78 cases. These results are considerably better than those obtained with any other drug tried by the senior author. The difficulties of obtaining satisfactory bark and of extraction of the alkaloids without producing decomposition, which renders them inert from the therapeutic point of view, are however considerable, and have been pointed out by these workers. The failures of kurchi alkaloids in the hands of Leake (1932) can thus be explained.

(Continued from previous page)

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During recent years some organic compounds of arsenic have been tried in chronic amoebiasis. Stovarsol or acetarsone (3-acetyl-amino-4-hydroxy-phenyl-arsinic acid) was the first compound of this series which could be given by the mouth and it was tried in this condition, but the drug showed no curative action whatsoever in intestinal amoebiasis. Treparsol (3-formyl-amino-4-hydroxy-phenyl-arsinic acid) has also been tried, but with no better results. Leake (1932) suggested that carbarson (4-carbamino-phenyl-arsinic acid) had better amoebicidal properties than any of the other arsenicals. Reed and his co-workers (1932) tried it in a small series of cases and found it to be very effective and non-toxic.

Carbarson belongs to the original series of organic arsenicals prepared and tested by Ehrlich and Berthelm as long ago as 1909 and has the chemical formula $H_2O_3AsC_6H_4NHCONH_2$ being 4-carbamino-phenyl-arsinic acid. It is a white crystalline solid without odour or taste; it is stable in air and contains 28.85 per cent of arsenic when anhydrous. It is practically insoluble in water, but dissolves in alkaline aqueous solutions; it melts at 174°C. It is readily absorbed after oral administration and is excreted in the urine at about the same rate as stovarsol. Experimentally it is less toxic than stovarsol and has more powerful amoebicidal properties, its 'therapeutic index' being about eight times as favourable as stovarsol. As it contains a substituted amino-group in the *para* position to the arsenic atom, its liability to injure the optic tract should be borne in mind. No untoward symptoms were, however, observed after continued administration of the drug to laboratory animals in doses within the therapeutic range. Carbarson has been recently put on the market by Lilly & Co., of Indianapolis, U. S. A., and is sold in pulvules of 0.25 gramme ($3\frac{1}{4}$ grains) each.

After reading about the encouraging results obtained by Reed and his co-workers the senior author tried the drug in a series of patients in the wards of the Carmichael Hospital for Tropical Diseases. The patients were mostly suffering from chronic amoebiasis and the majority of them had had repeated attacks of dysentery. The drug was prescribed in doses of 0.25 gm. twice daily for 10 consecutive days in gelatine capsules by the mouth. The patients were kept on ordinary diet and, except a saline purgative whenever required to relieve constipation, no other drug was given.

The criterion of cure applied in this series was five or more negative examinations of the stools on different days after the cessation of all treatment. As has been pointed out in a previous paper, it is fully realized that it cannot be claimed that all such cases were really cured. However it is the best criterion that can be practically employed and from experience we know that five negative examinations indicate

in most cases a favourable prognosis if not a definite permanent cure. The difficulty of keeping the patient in the hospital when once the acute symptoms are relieved is very great, so for all practical purposes we had to accept this criterion. Whenever possible more examinations were made.

The records of 31 cases in which the drug was tried are given in a table which is self-explanatory. Out of 31 patients 23 (74.2 per cent) were cured, in 4 (12.9 per cent) the drug failed and in 4 (12.9 per cent) the result was indeterminate. As regards the indeterminate cases, although the patients left the hospital before the usual five examinations of the stools could be carried out, considerable improvement was noticed in their general condition after the treatment. A perusal of column 3 will show that the majority of the patients had suffered from the disease for long periods, and that many of them showed cystic forms of *E. histolytica* and had Charcot-Leyden crystals in their stools. The separate cure rates in vegetative and cystic forms of infections are given below and it will be seen that the drug is equally effective in either condition.

	Total	Cures	Indeterminate	Failures
Vegetative	11	8 (72.8%)	2 (18.2%)	1 (9%)
Cystic	20	15 (75%)	2 (10%)	3 (15%)

The proportion of probable cures to failures in this series is 5.75:1, as compared with 3.5:1 obtained by Knowles (1928) with emetine bismuthous iodide in a similar series of chronic cases.

Among the failures it is interesting to note that out of four cases only one had vegetative forms of *E. histolytica* and three had the cystic form. Some of the patients were infected with bacillary dysentery also, in addition to the amoebic infection. These were the most difficult to cure, but a course of autovaccine given either preceding or along with carbarsone treatment often brought about a cure. In case no. 27, carbarsone failed, but extractum kurchi liquidum with liver extract was effective. The usual course of carbarsone failed to cure case no. 7, but a cure was effected by a course of emetine bismuthous iodide 2 grains daily for 10 days.

It may also be noted here that in this series no untoward symptoms of any kind were produced either on the eyesight (due to the *para* position of the substituted amino-group), on the gastro-intestinal tract, or on any other organ or tissue of the body, by administration of the drug in doses of 0.25 gramme ($3\frac{3}{4}$ grains) twice daily for 10 days. Even those patients who were not cured improved in health generally, on account of the tonic and stimulating effects of arsenic on the system. Continuation of the drug for longer periods is now being tried in patients who have failed with the usual course of 10 days.

TABLE

No.	Name	Race, sex and age	Duration and previous treatment	Laboratory findings before treatment	Treatment	Laboratory findings after treatment	REMARKS
1	K. P. ..	H., M., 22	1 year; emetine	<i>E. h. veg.</i> , C.-L. crystals, <i>B. lactis aerogenes</i> .	Carbarsone 0.25 gm., b.d., for 10 days.	Scanty <i>E. h. veg.</i> C.-L. crystals.	Failed.
2	B. R. ..	H., M., 26	2 years	<i>E. h. veg.</i> and cyst. C.-L. crystals.	Do.	Negative 6 exams.	Cured.
3	A. A. ..	M., M., 28	1½ months	Scanty <i>E. h. veg.</i> and cyst, H. W. and trichuris ova, <i>B. pseudo-carolinus</i> .	Do.	Do.	"
4	A. H. ..	M., M., 22	1½ years; emetine	<i>E. h. veg.</i> and cyst, giardia cyst, <i>Trichomonas hominis</i> .	Do.	Do.	"
5	H. C. P. ...	H., M., 44	2½ months	<i>E. h. veg.</i> , H. W. ova, giardia cysts.	Do.	Do.	"
6	R. ..	H., M., 40	7 years	<i>E. h. cyst</i> , H. W. and trichuris ova.	Do.	Negative 5 exams.	"

TABLE—contd.

No.	Name	Race, sex and age	Duration and previous treatment	Laboratory findings before treatment	Treatment	Laboratory findings after treatment	REMARKS
7	H. C. G. ..	A. I., M., 40	8 emetine	<i>E. h.</i> veg. and cyst.	I. Carbarsone 0.25 gm., b.d., for 10 days. II. Do. III. E. B. I. grs. ii, daily for 10 days.	<i>E. h.</i> veg. and cyst, giardia cyst, C.-L. crystals. <i>E. h.</i> veg. and C.-L. crystals. Negative 8 exams.	Failed. Cured with E. B. I.
8	B. S. ..	A. I., M., 5	4½ years	<i>E. h.</i> veg.	Carbarsone 0.075 gm., b.d., for 10 days.	Negative 6 exams.	Cured.
9	S. K. M. ..	H., M., 18	Originally admitted for malaria.	<i>E. h.</i> cyst. C.-L. crystals. <i>E. nana</i> cyst. Sputum: pneumococci, <i>M. catarrhalis</i> and short streptococci.	Carbarsone 0.25 gm., b.d., for 10 days.	Do.	"
10	R. B. M.	H., M., 28	10 months	<i>E. h.</i> cyst, C.-L. crystals, microfilaria, <i>B. meta-alkaligenes</i> .	Do.	Do.	"
11	T. A. K. ..	M., M., 50	12 days	<i>E. h.</i> veg., <i>B. proteus vulgaris</i> , H. W., ascaris and trichuris ova.	Do.	Do.	"
12	N. C. M. ..	H., M., 38	2 weeks	<i>E. h.</i> veg., <i>Trichomonas hominis</i> . H. W. ova. <i>B. lactis aerogenes</i> .	Do.	Negative 1 exam.	Indeterminate.
13	N. B. ..	M., M., 25	Originally a case of reticulo-endotheliosis.	<i>E. h.</i> veg., H. W. and ascaris ova.	Do.	Negative 6 exams.	Cured.
14	L. D. ..	H., F., 30	Present attack 4 months. Another attack two years ago.	<i>E. h.</i> cysts. H. W. ova.	Do.	Do.	"
15	A. A. ..	M., M., Ch., 6	Originally admitted for fever with enlarged spleen down to the umbilicus and liver 1½" below costal margin.	Scanty <i>E. h.</i> veg. urobilin.	Carbarsone 0.08 gm., b.d., for 10 days.	Negative 6 exams.	"
16	A. E. C. ..	A. I., F., 22	Irregular temperature for a month following an attack of enteric (<i>B. paratyphosus</i>).	Very scanty <i>E. h.</i> veg.	Carbarsone 0.25 gm., b.d., for 10 days.	Do.	"
17	A. B. ..	H., M., 24	Originally admitted for fever with enlarged spleen.	Scanty <i>E. h.</i> cysts, giardia and H. W. ova.	Do.	Do.	"

TABLE—contd.

No.	Name	Race, sex and age	Duration and previous treatment	Laboratory findings before treatment	Treatment	Laboratory findings after treatment	REMARKS
18	N.K.T. ..	E., F., 31	4 years.	<i>E. h.</i> veg., <i>B. pseudo-carolinus</i> and <i>B. flourescens</i> .	I. E. B. I. (vomited twice). II. Carbarsone 0.25 gm., b.d., for 10 days. (<i>B. pseudo-carolinus</i>).	Negative 3 exams.	Indeterminate.
19	H.N.C. ..	H., F., 31	Pain epigastric region and waist 12 years. Pneumonia, 12 years ago.	<i>E. h.</i> cysts. Pneumococci, Gram-negative bacilli in sputum.	I. E. B. I. (vomited twice). II. Carbarsone 0.25 gm., b.d., for 10 days and auto-vaccine.	Negative 4 exams.	"
20	S. C. ..	A. I., F., 9	Originally admitted for impetigo; suffered from dysentery when she was only a small baby.	<i>E. h.</i> veg. and cyst. Trichuris ova, <i>B. asiaticus</i> .	Carbarsone 0.25 gm., b.d., for 10 days.	Negative 6 exams.	Cured.
21	S.R.G. ..	H., M., 36	Duration of the present attack, 5 years. Dysentery in 1925 also. Liver tender. Indigestion present. Losing weight.	Scanty <i>E. h.</i> veg. and cyst. Blastocystis.	Carbarsone 0.25 gm., b.d., for 10 days.	Negative 6 exams.	"
22	B. J. ..	A. I., F., 23	Suffered from dysentery when she was 8 years old. Weak and wasted muscles of the right leg and constipation, 9 years.	<i>E. h.</i> and <i>E. coli</i> (veg. and cyst). Blastocystis.	Do.	Do.	"
23	S. ..	H., M., 7	2 years, liver enlarged.	<i>E. h.</i> veg., ascaris ova.	Do.	Do.	"
24	B.R.S. ..	H., M., 9	Pain right hypochondriac region, progressive loss of weight, dyspepsia, 4 years, liver enlarged.	Scanty <i>E. h.</i> veg. and cyst. Blastocystis.	Do.	Do.	"
25	H. J. ..	A. I., M., 11	Originally admitted for low fever, 1 month. Spleen enlarged.	<i>E. h.</i> veg. and cyst. C.-L. crystals. Blastocystis, ascaris and trichuris ova. B. T. rings, trophozoites and scanty gametocytes.	Do.	Do.	"
26	C.C.S. ..	H., M., 30	4 years; last attack 3 months back. Spleen and liver enlarged.	<i>E. h.</i> veg. and cyst, trichuris ova, enterococci.	Do.	<i>E. h.</i> veg. and cyst.	Failed (but cured with kurchi).

TABLE—concl'd.

No.	Name	Race, sex and age	Duration and previous treatment	Laboratory findings before treatment	Treatment	Laboratory findings after treatment	REMARKS
27	R.	E., F., 55	Dysentery last year. Pain right hypochondriac region 3 or 4 months.	Scanty <i>E. h.</i> cysts	I. Carbarsone 0.25 gm., b.d., for 10 days. II. Extract kurchi liquid 5i, b.d., for 10 days and liver extract, one phial, b.d., simultaneously.	Negative. 6 exams.	Cured.
28	W. G.	E., M., 34	6 months. Emetine, stovarsol outside.	<i>E. h.</i> cyst. <i>B. pseudo-carolinus</i> , <i>B. asiaticus</i> .	I. Carbarsone 0.25 gm., b.d., for 10 days. II. Autovaccine (<i>B. pseudo-carolinus</i>) 2 courses.	Negative 8 exams. on practically consecutive days; negative again after a fortnight.	Cured.
29	R.	H., M., 25	Pain right hypochondriac region.	<i>E. h.</i> cysts. <i>H. W.</i> ova. Fine colonies of yeasts. Sputum: pneumococci <i>M. catarrhalis</i> , yeasts, etc.	Carbarsone 0.25 gm., b.d., for 10 days.	Negative 6 exams.	"
30	J.	E., F., 24	Dysentery in September last, was treated with emetine with clinical improvement. For the last one month getting pain in abdomen. Had dysentery 3½ years ago.	Scanty <i>E. h.</i> cysts. <i>B. pseudo-carolinus</i> .	Do.	Negative 3 exams.	Indeterminate.
31	S.	E., F., 27	3 years.	<i>E. h.</i> veg., blastocysts.	Do.	Negative 6 exams.	Cured.

Abbreviations used:—

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|-----------------------|-----------------------------------------------|-------------------------------------------|
| A. I. = Anglo-Indian. | H. W. = Hookworm. | C.-L. crystals = Charcot-Leyden crystals. |
| E. = European. | <i>E. h.</i> = <i>Entamoeba histolytica</i> . | E. B. I. = Emetine bismuthous iodide. |
| M. = Mohammedan. | Veg. = Vegetative. | |
| H. M. = Hindu male. | Cyst. = Cystic. | |
| H. F. = Hindu female. | | |

Summary and conclusion

1. Carbarsone (4-carbamino-phenyl-arsinic acid) belongs to the series of organic arsenicals originally produced by Ehrlich in 1909. It is a white crystalline solid containing 28.85 per cent of arsenic.

This compound has amœbicidal properties and is given in doses of 0.25 gm. (3¾ grains) in gelatine capsules twice daily. In a series of 31 cases a ten-day course cured 23 patients (74.2 per cent), 4 (12.9 per cent) remained indeterminate, and 4 (12.9 per cent) remained uncured. The proportion of probable cures to failures in this series was 5.75:1, as compared with 3.5:1 obtained by Knowles in a similar series with emetine bismuth iodide, and 3.16:1 obtained by Acton and Chopra with kurchi bismuthous iodide.

The drug produced no untoward effects in the doses administered, and is worthy of further trial in the treatment of chronic intestinal amœbiasis.

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