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AMOEBIC DYSENTERY AND ITS EFFECTIVE TREATMENT*

A CRITICAL STUDY OF 535 CASES

BY

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The aim of the present investigation has been to discover the best method of treating intestinal amoebiasis and of eradicating this infection.† 535 cases have been selected for this study out of numerous records of clinical amoebiasis during a period of twenty years. Those only have been included in which *Entamoeba histolytica* or its cysts have been demonstrated by personal observation. No metastatic complications of amoebiasis have been considered unless accompanied by manifestations of active amoebic dysentery.

Of the cases 450 were in men and 85 in women; with the exception of 8 Indian seamen all the patients were Europeans. They were derived from sixty-four countries, though the great majority were from India, Ceylon, West Africa, China, and Malaya; smaller numbers hailed from other parts of Africa, from Egypt to the Cape, including the Canaries, Cape Verde Islands, and Mauritius. In Europe a few were infected in Northern France, Germany, Austria, Greece, South Russia, and Malta. From America cases came mostly from the West Indies and the South American republics. From Australia there was one example, from New South Wales; from England one indigenous infection.

This case occurred in a stevedore in the London docks who had been suffering from supposedly ulcerative colitis. He had never been out of England, but had worked for twenty years on the wharves, where he had probably contracted amoebiasis from association with Indian seamen.

Most cases originated between the second and fourth decades of life, a small proportion (43) between the fifth and sixth, and only 8 above that age. There were 8 under 20 years old, the youngest being 7½ (although the infection had been acquired five years earlier). Amoebiasis therefore appears to be mostly a disease of adult life: European children are seldom affected. It is usually contracted from contaminated water. Thus 10 in this series were employees of a cable company from St. Vincent (Cape Verde Islands), where the evidence of infection from stored and contaminated water was found to be almost conclusive.

Diagnosis

The following is a summary of the findings:

Diagnosed by <i>E. histolytica</i> in scrapings from ulcers in rectum ..	26
Diagnosed by active <i>E. histolytica</i> in faeces ..	222
Diagnosed by <i>E. histolytica</i> cysts in faeces (in 17, precystic forms together with cysts) ..	287

In many cases *E. histolytica* cysts were associated with *Giardia intestinalis*, *Iodamoeba buetschlii*, *Endolimax nana*, *Entamoeba coli*, active and cysts. In no instance were active *E. histolytica* and cysts found simultaneously in blood and mucus stools. It is important to note that in 26 cases diagnosis was rendered certain from scrapings made from

amoebic ulcers in the bowel, whereas no confirmatory evidence had been forthcoming by simultaneous faeces examinations.

Sigmoidoscopy was performed in 258 cases, amoebic ulcers and other characteristic lesions being demonstrated in 234. In 77 cases active entamoebae were recognized in scrapings; in 24 (9.3%) the mucosa had a normal appearance. Routine sigmoidoscopy has therefore proved its value as a means of securing positive diagnosis. Thus:

An officer aged 27 who had for long been regarded as suffering from ulcerative colitis was seen in June, 1934. The faeces had been examined microscopically on many occasions, with a negative result. Sigmoidoscopy revealed ulcerated mucosa, and in scraping active *E. histolytica* was seen. It transpired that up to 10 years of age he had lived in Mauritius, where he had suffered from mild dysentery, but since then had not been abroad. The latent period of this infection was therefore seventeen years.

Complicating Conditions

Many other complicating infections were recorded, such as: malaria (30 cases), kala-azar, trypanosomiasis, filariasis (*A. perstans* 3, *Loa loa* 1), ankylostomiasis, oxyuriasis, ascariasis, bilharziasis (*S. mansoni* 2), sprue (8), cardiac complications (4), *B. coli* bacilluria (5), liver abscess (6), amoebic infection of the skin (1), syphilis (4), renal calculus (3), fistula in ano, rectal abscess, fibroid phthisis, pneumonia, tuberculous mesenteric glands, etc. Two cases in which the patient was pregnant (seven months and six weeks respectively) were cured by E.B.I. treatment.

Clinical Notes

Amoebic dysentery is usually chronic in nature and erratic in its course. It is particularly benign, and seldom dangerous to life. There was only one death in this series, in a patient who was moribund when the diagnosis was made:

Though the onset of the fatal illness was sudden and death took place within three days, it is probable that the patient had been infected for a considerable period. He was a ship's carpenter who had sailed to the Tropics for many years. At necropsy extensive ulceration and necrosis of the large intestine were found, as well as five liver abscesses.

The great majority are apyrexial. Fever usually denotes subacute hepatitis, which accounted for 30 in this series, but occasionally an alarming pyrexia, which may best be termed "amoebic fever," may be noted.

A seaman on his arrival from Sierra Leone (July, 1940) had been ill for sixteen days with high fever, headache, bone pains, and other signs of toxæmia. His general condition suggested typhoid. There were occasional attacks of diarrhoea and meteorism. No amoebae could be demonstrated in the faeces, though sigmoidoscopy revealed extensive ulceration of the rectal mucosa, containing active *E. histolytica*. Response to treatment was almost immediate (see Chart).

* Based on the Lumleian Lectures for 1941.

† The results of treatment are given in a series of tables at the end of this paper.

Classification.—Acute cases with bloody diarrhoea and distressing symptoms are rare. There are records only of 4 in the present series, including the fatal case already recorded. 244 could be classified as subacute, with blood and mucus in the stools, diarrhoea, abdominal pains, and urgent symptoms; but the majority (287) were chronic, with intermittent diarrhoea, the faeces containing *E. histolytica* cysts and precystic forms presenting comparatively

was noted only in 7 cases; meteorism and flatulency occurred in 45. Vomiting is certainly not a usual feature of amoebiasis, and was recorded in 3 only. It is necessary to emphasize these features, as there appears to be an impression that amoebic dysentery may be ushered in by violent gastro-intestinal disturbances.

Solitary Indurated Amoebic Ulceration of Rectum.—Two instances of remarkable localization of amoebic ulceration have been revealed. Both occurred in ex-soldiers, and the process had taken many years to develop. One had contracted his infection in France in 1916, though urgent symptoms first showed some 21 years later; the second, from India, was of 10 years', standing. These ulcers, palpable by digital rectal examination, were deep and excavated, with hard and craggy margins suggesting malignant growths. From the surface scrapings active *E. histolytica* was recognized. Both cases yielded satisfactorily to anti-amoebic treatment.

Rectal prolapse occurred in 3 cases, 2 of which could be attributed to straining; the prolapse was rectified on appropriate anti-amoebic treatment.

Appendicitis.—Chronic inflammation of the appendix may complicate active amoebiasis. In the present series 29 cases (5.4%) of appendicitis necessitated operation, but in no single instance were amoebae demonstrated in the microscopical sections of this viscus.

Subclinical Cases.—However exhausting the physical examination, there still exists a residuum presenting no outward physical signs beyond the fact that the patient may complain of malaise and fatigability. Sometimes the complexion assumes a muddy colour, the tongue is coated, and the skin may lose its normal elasticity. The true nature would certainly be missed in the absence of a routine microscopical examination of the faeces.

Latency.—The chronicity of amoebiasis is compatible with long periods of quiescence or latency, during which the patient enjoys uninterrupted good health, and may veritably believe that he is cured, when all the while there exists a residual focus of infection in the large intestine which may light up, producing somewhat alarming symptoms. In this series there are records of some 11 cases in which the quiescent period lasted from five to twenty-two years.

Treatment

A large number (259, or 48.5%) had at some previous time undergone emetine injection therapy, either alone or combined with other drugs. The figures are impressive, but they certainly do not support the assumption that hypodermic injections of emetine are a certain cure. In chronic cases it is especially necessary to emphasize this, because it is generally assumed that emetine is so specific for amoebiasis that it will cure any case, however chronic. That hypodermic emetine treatment controls the urgent clinical manifestations there cannot be any reasonable doubt, but it certainly does not, in the majority of instances, eradicate the infection. This is evident from the figures (Table II). There appears to be ample evidence that, so far from finally curing the patient, this practice tends to render the amoebae emetine-fast and final cure thereby much more difficult to attain (Table II).

There were 7 emetine intoxications in the series. Taking into consideration the number of cases and the intensive emetine injection therapy to which some of them had been subjected, this is not a high proportion. Emetine intoxication may declare itself by asthenia, mental depression, low blood pressure, cardiac irregularity, desquamation of the skin, brittleness of the nails, painful muscles (myositis), and, finally, by neuritis. In extreme degrees there is some paresis of the legs with slight foot-drop, cold clammy skin, abolition

few indefinite physical signs. In 15 the chief complaint was chronic diarrhoea, without passage of either blood or mucus, which supports a suggestion that this type of case might better be termed "amoebic diarrhoea." Included with the chronic cases are those symptomless forms, numbering 15 (2.8%), without suggestive medical history or physical signs, but which harboured *E. histolytica* cysts and which had become symptomless "cyst carriers." Intestinal amoebiasis is compatible with average good health, as is borne out by the following figures. The average duration before treatment was four and a half years. In 24 the disease had already persisted over sixteen years, the extreme being thirty years; only 25 (4.7%) were investigated and treated during the first attack. The periodic supervention of relapses is a striking feature: in the majority it is difficult to keep count of these recrudescences, but the average number in 245 cases worked out at 3.3.

Physical Signs.—Distinctive physical signs may be few. Enlargement of the liver is fairly constant when complicated by hepatitis (76). The caecum and transverse colon were thickened in 128, but pericolic infiltration of the sigmoid, which is the more obvious, was found in 212. In one there was an elongated palpable tumour, which from its physical characters had been mistaken for carcinoma of the sigmoid. Loss of weight is rarely encountered in amoebiasis, however long-standing, and this was recorded in 61 cases (ranging from 10 to 42 lb.). Two patients suffered from obesity. In only one instance had emaciation been so considerable as to suggest the possibility of carcinoma. Intermittent haemorrhage from the large intestine may occasionally occur. In 4 instances active *E. histolytica* were demonstrated in melaena, thus rendering diagnosis certain. Constipation, alternating with diarrhoea (noted in 4), may be the outstanding feature, not incompatible with a diagnosis of amoebiasis.

Symptoms.—Localized deep abdominal pain and tenderness on palpation over caecum and sigmoid are most frequent (173). On the other hand, tenesmus, which is such a feature of bacillary dysentery, is usually absent, and

of the deep reflexes, and usually a fair degree of paraesthesia. All patients who showed intoxication had been subjected to prolonged courses of emetine injections and had received a total amount ranging from 70 to 130 grains.

Occasionally emetine may attack one particular group of muscles, causing progressive wasting and eventually a state resembling progressive muscular atrophy, as in the following case :

This patient, seen in 1920, appeared to be sensitive to emetine. He had suffered for four years from recurrent dysentery, for which he was treated by emetine injections ; but after a course of 27 grains of emetine bismuth iodide wasting resembling progressive muscular atrophy developed, affecting the trapezius, supraspinatus, infraspinatus, and deltoid muscles. Function was not fully restored till after a period of massage and electric treatment lasting three months.

Emetine Bismuth Iodide (E.B.I.).—The outstanding merit of this drug is its effect upon the cysts of *E. histolytica*. The maximum individual dose for an adult is 3 grains, given over a period of ten nights ; but recent experience has shown that a smaller dose—2 grains—is equally effective and causes less physical and mental depression. As is well appreciated, E.B.I. is best given in hard gelatin capsules on an empty stomach about 10 p.m.—3½ hours after the last meal. Luminal is probably the most effective sedative to combat nausea and possible vomiting : 1 grain at 9 p.m. usually suffices, but for refractory cases a better method is 1 grain at 8 p.m. and a further 1/2 grain an hour later. Occasionally allonal, or 10 minims of tinct. opii or nepenthe, is more satisfactory. When in the form of hard tablets coated with stearin, E.B.I. is apt to be passed unabsorbed in the faeces. Therefore to ascertain that it has been properly absorbed becomes an important factor in its administration. In this series 114 cases were treated with E.B.I. in doses totalling from 20 to 40 grains, and 7 (6.1%) relapses were registered. Some proved singularly resistant, and 3 were still uncured after nine separate courses of the drug.

Emetine Periodide (E.P.I.).—Introduced in 1923, this is less toxic than E.B.I. and consequently better tolerated, and can therefore be given in larger amounts. It has been customary to combine it with ox-bile tablets of 5 grains. Of 13 cases treated with E.P.I. in courses totalling 40 to 72 grains (maximum tolerated dose, 6 grains daily), 5 (46%) subsequently relapsed. Though better tolerated than E.B.I., it cannot on this evidence be regarded as being as efficacious.

Auremetine.—This drug, a compound of auramine (an aniline dye) and emetine, has been tried out intermittently since its introduction in 1923. The dose is 3 to 4 grains daily for ten days, given in the same manner as E.B.I. Five cases were so treated ; the toxic effects were considerable, and all subsequently relapsed.

Quinoxyl (Synonyms: yatren, chiniofon, anayodin).—This drug has been employed since 1925. The combination of oxyquinoline-sulphonic acid and iodine, when given in pill form by the mouth, did not prove satisfactory. Rectal retention enemata, 2½% in 200 c.cm., usually preceded by an enema of 2% sodium bicarbonate, are well tolerated and can be retained from four to eight hours. In refractory cases the strength has been doubled to 5% (Table III) without any disagreeable effects. Beyond a slight erythematous rash no signs of intolerance have been observed. The action of this drug on amoebic lesions can be readily observed by periodic sigmoidoscopic examinations. My experience in 35 cases treated by quinoxyl by mouth and rectum led me to believe that it is especially useful in those resistant to E.B.I. ; but in freshly occurring

infections it was not so successful. Relapses were subsequently registered in 8 (22.8%).

Combined treatment as introduced by me consists of quinoxyl retention enema by day and E.B.I. by night (Table I). By this combination it is thought that the infection is assailed from above by emetine bismuth iodide and from below by quinoxyl. The treatment is continuous, and is maintained for ten to twelve days. A total of 361 cases were treated in this manner: 323 had E.B.I. (20 to 30 grains) as well as quinoxyl during the course. The relapse rate of this series was 3.7%. Of those (38) who proved at first intolerant of E.B.I., E.P.I. in combination with quinoxyl was substituted, and 5 (13.1%) relapsed later. These refractory cases were eventually cured by further intensive treatments of E.B.I. and quinoxyl. Every effort has been made to follow up the after-results, and the majority have been examined at intervals for ten years and even longer (Table III), and these results verified. For the success of this treatment it is not necessary to restrict the dietary. Patients may be permitted a fairly generous breakfast and an equally generous lunch, but no supper.

Stovarsol.—In this series 8 were treated with 80 grains of stovarsol (8 grains for ten days), and 7 of these subsequently relapsed, but there were five instances of stovarsol poisoning. Signs of intoxication were a rosy urticarial rash, with pyrexia—a combination which may resemble German measles.

In one resistant case the patient, who had on his own initiative dosed himself for over one month, developed exfoliative dermatitis and subsequently arsenical pigmentation of the skin and rectal mucosa.

Carbarsone.—Carbarsone has enjoyed much popularity in America. The dose (4 grains twice daily for ten days) is the same as for stovarsol. It proved on trial no more effective, and there appears to be the same danger of arsenical poisoning. In 3 cases relapse took place directly a course had been completed. Regarding the curative value of carbarsone, a particularly acute case of amoebic dysentery was investigated in 1940.

Under medical direction the man had taken two pulvules (8 grains) daily for one month ; nevertheless numerous unhealed amoebic ulcers, in which active *E. histolytica* were demonstrated, were seen in the rectal and lower sigmoid regions. He was subsequently completely cured by E.B.I. and quinoxyl.

Other Drugs Investigated

Enterovioform, containing 37.5% of iodine in gelatin capsules (4 grains), was given three times daily for ten days to 2 chronic cases ; these almost immediately relapsed. **Rivanol** was given in the form of retention enema of 1/2,000 solution, and 500 c.cm. was injected and retained. This substance has a soothing action on the mucous membrane, but appears to have no effect on the amoebae. **Gavano** (Bayer)—probably cephaeline—in tablet form three times daily for six days, was tried in 3 chronic cases with *E. histolytica* cysts, but it had apparently no action. **Chaparro amargosa**, an extract of the bark of *Castela nicholsoni*, has been extensively used in Mexico. In 3 cases it was tried as a retention enema for ten days. The results were inconclusive. Trials were also given to *conessine*, *kurchine hydrochloride*, and *kurchi bismuth iodide*, as advocated by H. W. Acton and R. N. Chopra (1933). No permanent cures were registered.

Conclusions

It became evident that in treating chronic intestinal amoebiasis the principle of "therapia magna sterilisans" has to be maintained. The employment of inefficient dosage of emetine and other drugs over a prolonged period

renders the infection eventually more difficult to eradicate. The following principles may be enunciated:

1. A fresh infection is more easy to eradicate than one of long standing.
2. The widely accepted practice of periodic injections of emetine, or even inadequate doses by the mouth of other emetine compounds, is not recommended, for it has been indicated that, so far from effecting a cure, this method tends to render *E. histolytica* emetine-fast.
3. Cases, however resistant, can eventually be cured, provided the course of anti-amoebic treatment is sufficiently thorough and prolonged.
4. Quinoxyl is a potent non-toxic drug, causing few disagreeable sequelae. In resistant cases of amoebiasis it produces the most permanent results in combination with emetine bismuth iodide. This treatment is usually well tolerated, provided that minutiae of dosage and timing are observed.

Results of Treatment

TABLE I.—Showing Nature of Anti-amoebic Treatment on 276 (51.5% of the Series) previously Untreated Cases (110 with Active Amoebae and 166 with Cysts)

Emetine bismuth iodide courses of 20 to 26 grains	29
Emetine periodide courses of 28 to 72 grains with tablets of fel bovinum	9
Quinoxyl pills (4 grains), plus quinoxyl retention enemata 2½%	18
Stovarsol 80 grains (cyst-carrier case)	1
Combined treatments:	
Emetine bismuth iodide 20 to 26 grains, plus quinoxyl retention enemata 2% (1 case, 5%)	198
Emetine periodide 20 to 30 grains, plus quinoxyl retention enemata 2½%	17
Auremetine 30 grains, plus quinoxyl retention enemata 2½%	4

Out of 276 cases there were only 4 (1.4%) uncured. Two definite relapses occurred one year later, and these were ultimately cured with further treatment. In 2 cases the result could not be followed up.

TABLE II.—Showing Effect of Emetine Injection Treatment on 259 (48.5% of the Series) Cases (138 with Active Amoebae and 121 with Cysts) prior to Parasitic and Clinical Relapse

Emetine injections ranging from 40 to 60 grains, given over a period of 4 to 6 months, in 2 cases reinforced by intravenous emetine	171
Emetine injections, plus 2 to 3 courses of emetine bismuth iodide, emetine periodide, or auremetine	67
Emetine injections, plus oral quinoxyl, stovarsol, carbarsone, or ipecacuanha	21

TABLE III.—Further Anti-amoebic Treatment of Emetine-injection-treated Cases Detailed in Table II

Emetine bismuth iodide courses of 30 to 40 grains	91
Emetine periodide courses of 30 to 70 grains with tablets of fel bovinum	6
Quinoxyl pills (4 grains), plus quinoxyl retention enemata 2½%	17
Stovarsol 80 grains, plus quinoxyl retention enemata 2½%	2
Emetol retention enemata	1
Combined treatments:	
Emetine bismuth iodide 19 to 30 grains, plus quinoxyl retention enemata 2½% (5% in 16 cases)	124
Emetine periodide 30 grains, plus quinoxyl retention enemata 2½%	17
Auremetine 30 grains, plus quinoxyl retention enemata 2½%	1

RESULTS OBTAINED IN THE SERIES OF TABLE III

Of these 259 there were 20 cases which relapsed still further, but all, with one doubtful exception, were eventually cured. The relapse rate was 7.7%. The following are typical resistant cases:

Case 1.—Infected in Tanganyika in 1917; continually relapsed after courses of emetine injections. Admitted to hospital 1920, 1922, 1923, for treatment with E.B.I., E.P.I., and ipecacuanha. Eventually cured in 1928 with full combined course of E.B.I. 30 grains and quinoxyl retention enemata 5% for ten days.

Case 2.—Infected in Nigeria in 1928; had numerous relapses in spite of emetine injections. Had amoebic hepatitis in 1935. Relapsed again after E.B.I. treatment. Eventually cured in 1936 with E.B.I. 20 grains and quinoxyl retention enemata 2½%. Reported up to 1941 in good health.

Case 3.—Had spent forty-two years in West and Central Africa. In 1925 suffered from amoebic dysentery and hepatitis,

controlled by emetine injections. In 1934 *E. histolytica* cysts were found in the faeces, and sigmoidoscopy revealed amoebic lesions. He was treated by E.B.I. 30 grains and quinoxyl retention enemata 2½%. Febrile attacks recurring in 1935, he was operated upon for cholecystitis, but instead a chronic intralobar abscess in posterior part of right lobe of liver was exposed. During convalescence an acute attack of amoebic dysentery developed, with active *E. histolytica*. This was finally cured by repeating the course of treatment with E.B.I. and quinoxyl 5%. He has remained in good health ever since. It is a matter for speculation why the treatment which appeared ineffective in 1934 was curative a year later.

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AMOEBIASIS—PULMONARY COMPLICATIONS

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Our experience in Natal leads us to believe that pulmonary amoebiasis is fairly common in the coastal belt, more particularly among the non-European population. It is our contention that whenever amoebic dysentery occurs pulmonary complications will be found in a high percentage of untreated cases. This is of great importance to the armies in the East. There is no doubt about the high incidence of amoebiasis in the population of Natal, as judged by the various hospital records. In 1939, for example, at the King Edward VIII Hospital for Natives, Durban, 1,520 cases of amoebic dysentery were admitted—i.e., one-tenth of the total admissions for the year. At the McCord Zulu Hospital in 1940, of 3,763 admissions 251 (6.7%) were cases of amoebic dysentery. Many of these cases had been wrongly diagnosed as pulmonary tuberculosis.

Amoebiasis of the lung may be primary or secondary. The primary form is comparatively rare; the latter form is much more frequent than is thought.

Primary Pulmonary Amoebiasis

Manson-Bahr (1940) states that in primary amoebiasis of the lung "the entamoebae reach the lung by direct embolism from the gut wall. Having gained the pulmonary circulation, they form consolidated nodules, which later break down into small abscesses."

Our cases have presented the following signs and symptoms: cough, sputum, haemoptysis, wasting, night sweats, evening rise of temperature—in fact, all those of pulmonary tuberculosis. The main points leading to a diagnosis of primary pulmonary amoebiasis were: (a) a careful history revealing no family or other known contact with a case of