THERAPY OF AMEBIASIS*

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INTRODUCTION

AMEBIASIS is a readily curable condition which responds promptly and nearly always completely to correct management. The commonest cause of the failure of treatment is faulty diagnosis due to the incorrect identification of *Entamoeba histolytica.* In many other instances, however, it results from erroneous assumptions regarding the pathogenicity of the parasite. This leads to treatment that is frequently inadequate, at other times excessive and, perhaps even more often, entirely irrelevant. Such assumptions have resulted in misleading claims of the efficacy of various amebicides and in neglect of the cardinal principle that treatment should be directed at the three possible sites where *E. histolytica* may exist. These sites are the bowel lumen, the intestinal wall and, systemically, particularly the liver.

The story of drug treatment in amebiasis reflects the background of changing concepts of the nature and pathogenicity of *E. histolytica.*

Modern knowledge of clinical amebiasis dates from the latter part of the last century, when the disease was clearly recognized as invasive, presenting with the often fatal conditions of amebic dysentery and hepatic abscess. Ipecacuanha had long been used in treatment[1] but the first and enduring landmark in treatment was the introduction of emetine hydrochloride by Rogers in 1912.[2] This drug proved to be life-saving and, although limited by toxicity, it has remained universally successful wherever severe amebiasis is encountered. However, despite its efficacy as a tissue amebicide, it frequently fails to eradicate amebas from the lumen of the bowel, and recurrence of symptoms is common. This is a major reason why amebiasis has gained the reputation of being a chronic, relapsing condition. In fact, resistance is not an inherent

*Presented as part of a *Symposium on Amebiasis* sponsored by The Tropical Disease Center, St. Clare's Hospital, New York, N. Y., and The Merck Company Foundation, Rahway, N. J., held at the Center, September 12, 1970.

property of the ameba and relapse is due to the limitations of many amebicides. Emetine hydrochloride alone is never adequate.

Oral preparations of emetine were introduced to achieve greater activity in the bowel lumen,[3] and they have yielded high rates of cure in intestinal amebiasis.[4] The combination of emetine hydrochloride with emetine bismuth iodide is still found adequate by many experienced physicians.[5] It is, however, an unpleasant medication and, in our experience, it regularly causes diarrhea. Nausea and vomiting are also frequent.

Shortly after World War I the view became prevalent, particularly in the United States,[6,7] that *E. histolytica* was an obligate pathogen which always invaded the tissues. Since infection was known to be common in temperate regions this implied that there were vast numbers of individuals in need of treatment. Consequently during the next two decades impetus was given to the development of drugs which would remove these amebas from the bowel. The number of such luminal amebicides produced is too numerous to list but prominent among them were oral arsenicals and quinoline derivatives. More modern preparations have appeared since World War II, of which diloxanide furoate is a notable example.[8] All are capable of eradicating lumen-dwelling amebas to a varying degree and have enjoyed a vogue in temperate countries for the treatment of symptomless and mildly symptomatic bowel infections, but all have been found inadequate where amebiasis is associated with a significant degree of tissue invasion.[9]

At this point it is relevant to digress in order to consider the problem of treating chronic bowel infections. Although the concept of *E. histolytica* as an obligate pathogen is no longer universally accepted[10] it continues to tempt practitioners to ascribe a wide range of symptoms to presence of the ameba. When specific treatment has failed to bring relief the drug is blamed. Should repeated courses of amebicides then be given for the long-since exterminated, innocent, and probably commensal amebas? Both practitioner and patient are often left with the conviction that "amebiasis" is a chronic and incurable condition. To achieve cure in such instances, education of the physician is more effective than amebicides for the patient. It is a sound general rule that when symptoms have failed to respond to a reputable amebicide the diagnosis should be questioned and search made elsewhere for the cause of the patient's complaints. Serological tests are invaluable in ascertaining if symptoms are likely to have been caused by *E. histolytica* but

there is some danger that the tests and not the patient will be treated. It should also be borne in mind that apparent response to an amebicide is not diagnostic of amebiasis. Many patients with other disorders, often of a psychosomatic nature, may appear to respond, although this is usually only temporary.

Nowadays the consensus is that in the vast majority of infected subjects *E. histolytica* is merely a commensal living within the lumen of the bowel.[11] In most temperate regions infected persons are extremely unlikely ever to suffer significant invasion of the tissue that results in disease. However, this can occur on rare occasions; thus many feel that treatment of such symptomless cystpassers or coincidental infections is justified. Others are concerned that this attitude opens the floodgates of indiscriminate treatment, encouraging the development of bowel neuroses and the neglect of other organic disease. Since it has not yet been shown that the presence of *E. histolytica* is ever actively beneficial, strong views against treatment under these circumstances are hardly tenable although there are greater priorities in medicine. But if amebicides are given, neither the physician nor patient should be in any doubt of the limited objectives of the therapy.

In regions where there is much invasive amebiasis commensal infections are also common. However, tissue invasion may be symptomless and, presumably, the chance of its taking place is greater in endemic areas. Moreover in such regions symptomless carriers may be the cause of invasive infections in others. Hence where invasive amebiasis is endemic the case for treating symptomless or possibly coincidental infections is stronger although the undesirable results of indiscriminate treatment are perhaps greater. "Amebaphobia" flourishes particularly in places where true invasive amebiasis is present to lend a background of authenticity to diagnostic claims that would otherwise be unconvincing if not absurd.

The end of World War II heralded the era of antibiotics in amebiasis. In 1945 Hargreaves[12] demonstrated the value of penicillin and sulphonamides in amebic dysentery. Soon after this it became evident that the tetracyclines were the most effective of all, acting on *E. histolytica* apparently indirectly by modifying the bacterial flora of the bowel.[13-16] The original tetracyclines remain the antibiotics of choice but relapse may occur after apparent cure, and no tetracycline is of value in hepatic amebiasis.[17]

TABLE I. AMEBIC DYSENTERY: RESULTS OF TREATMENT AND SITE OF ACTION OF AMEBICIDES

Therapy	*Bowel lumen*	*Bowel wall*		*Percentage cure*
Emetine HCL or Dehydroemetine	−	+	+	30-50
Emetine HCL + E.B.I.	+	+	+	92
Luminal amebicides	+	−	−	20-50
Oral tetracycline	+	+	−	97
Chloroquine	−	−	+	10
Tetracycline + luminal amebicide + chloroquine	+	+	+	98
Tetracycline + luminal amebicide + emetine HCL or dehydroemetine	86	+	+	+

In contrast Conan[18] showed that chloroquine was effective in amebic abscess of the liver although it has little activity in the bowel. As a less toxic alternative to emetine the drug achieved wide usage but it is inferior.[19, 20] Nevertheless, it is of value as a supplementary medication.[21]

The synthetic preparation dehydroemetine appeared in 1959.[22] Because of more rapid excretion and a more favorable liver-heart concentration ratio, it was hailed as an advance on natural emetine.[23] While some doubt has been cast on claims of reduced toxicity,[24] in practice the drug is a satisfactory alternative to emetine.[25] However, it possesses precisely the same limitations.

Until approximately five years ago these were the major drugs available for treatment. Our findings in 20 years of controlled trials in Durban are summarized in the two accompanying tables.

No single drug was adequate and the selective actions of all were a source of confusion, but when they are used in correct combination excellent rates of cure can be obtained. Although it is by no means essential that these preparations should be entirely abandoned, recent developments have lessened their value for, compared to the newest drugs, such combinations are more complicated and tedious to use, and some occasionally exhibit toxicity.

In 1964 a preliminary report of the effect of niridazole in amebic abscess of the liver[26] led to the introduction of a new series of compounds in therapy. It was soon demonstrated that niridazole alone was

TABLE II. AMEBIC LIVER ABSCESS: RESULTS OF TREATMENT

*Treatment**	*Percentage cure*
Emetine 65 mg. × 10 days	88
Emetine 65 mg. (2 courses)	100
Dehydroemetine 80 mg. × 10 days	88
Dehydroemetine 80 mg. (2 courses)	89
Chloroquine × 28 days	71
Emetine 65 mg. + chloroquine	98
Dehydroemetine 80 mg. + chloroquine	100

*In all instances a luminal amebicide was also given and, when concomitant dysentery was present, tetracycline was added.

capable of curing both intestinal and hepatic amebiasis, but an undesirable degree of toxicity was evident.[27]

It was not long, however, before another nitroheterocyclic compound was found to yield even better results. This is the nitroimidazole derivative metronidazole. The drug had been safely and widely used since 1959 for the treatment of trichomoniasis, but the first successful clinical trials in amebiasis did not appear until 1966.[28] Since then favorable results of numerous and extensive trials, particularly in invasive amebiasis, have been reported.[29, 30] In appropriate dosage metronidazole has proved equally effective in childhood amebiasis.[31-33] At present metronidazole is unique as a safe, single, direct-acting amebicide with activity at all sites. It is the treatment of choice in most forms of amebiasis.

Much of our most recent work on metronidazole in Durban has been concerned with duration of the treatment. The almost traditional viewpoint that amebiasis is often a chronic and relapsing condition led to the belief that prolonged and often repeated courses of amebicides were necessary to achieve cure. We believe that this is really a reflection on the adequacy of the drugs and that if a sufficient concentration of an effective preparation can be achieved duration of treatment can be short. We find that a single large dose of 2.0 to 2.4 gr. of metronidazole is capable of curing a high proportion of patients with amebic dysentery or hepatic abscess. If this dose is repeated on a second day the rate of

cure is higher and appears adequate in many regions. In the severe cases encountered in Durban three such doses yield results which are similar to those obtained by our previously recommended, optimal five-day course.[34, 35] There is now a choice of regimens available.

It is important to realize that metronidazole is highly absorbed; hence smaller doses are effective in the tissues than in the intestinal lumen. Good results have been reported in symptomless cyst-passers and mild dysentery,[36] but the temptation to use too small a dosage should be avoided. Newer nitroheterocyclic compounds are likely to appear in the near future, but it must be borne in mind that laboratory evidence of increased activity is liable to be offset by increased absorption. Higher blood and tissue levels will result but the concentration in the intestine may remain inadequate.

For detailed accounts of the modern management of various forms of amebiasis and its complications reference should be made to other publications,[9, 37-40] but our routine drug therapy can be summarized as follows:

Symptomless intestinal amebiasis. There is a wide choice of luminal amebicides. Diloxanide furoate, 0.5 gr. thrice daily orally for 10 days, is satisfactory. Alternatively metronidazole, 400 to 800 mg. thrice daily for 5 days, may be used.

Chronic nondysenteric intestinal amebiasis. Mild cases with minimal or no invasion of tissue may respond to luminal amebicides but as a general rule treatment should be as for amebic dysentery.

Amebic dysentery. Metronidazole, either a single dose of 2.0 to 2.4 gr. on three successive days, or 800 mg. thrice daily for 5 days.

Hepatic amebiasis. Metronidazole, 400 mg. thrice daily for five days, or a single dose of 2.0 to 2.4 gr. on two or three successive days. While small abscesses repond to drugs alone, closed aspiration remains an essential part of management in many cases. The indications and technique for this procedure are well described.[9, 37, 40-41] Nevertheless, inadequate drainage is the commonest reason for failure of treatment and relapse.

Relapse in intestinal amebiasis. Because of the tendency of many drugs to convert patients to a temporary state of symptomless cyst-passing with eventual relapse, examination of stools, including a concentration technique, should be performed one month after completing treatment and, if possible, again after two months. Where circumstances

permit, search should be made for a source of reinfection in all adequately treated patients who suffer relapse. Not infrequently the source is a member of the same household with a symptomless infection.

Prophylaxis. Diarrhea is a common affliction among visitors to warm climates. It has been repeatedly shown that *E. histolytica* is not a significant cause of this condition, yet large quantities of luminal amebicides are still consumed for both prophylaxis and treatment. It may be, although I doubt it, that some of the drugs are of value in preventing such traveler's diarrhea, but it needs to be stressed that this is not amebiasis.

In regions of endemic amebiasis there is always the possibility that an individual may become infected but the chance is small. In Durban, where invasive amebiasis is highly endemic in the black community, both infection and disease are rare in whites. To accept the recommendation that such individuals, whether resident or visitant, should take prophylactic amebicides is absurd. It is a gross exaggeration to suggest that the need for prophylaxis against amebiasis is in any way similar to that for protection against a condition such as malaria.

The only solid indication for prophylaxis that I can envisage is in sudden outbreaks of invasive amebiasis. These are rare but they occur in association with contamination of drinking water by sewage.

Conclusions

The advent of metronidazole has greatly simplified therapy and has proved of particular value in the treatment of invasive amebiasis. However, the drug should not be looked upon as a simple and safe cure-all to be used indiscriminately in place of accurate diagnosis. Although the necessity to resort to the older amebicides has diminished, they need not be entirely abandoned. Indeed, in some instances parenteral emetine preparations remain essential and life-saving. Nor should the availability of metronidazole cause us to neglect such basic principles of management as fluid and electrolyte replacement in dysentery and the need for aspiration in hepatic abscess.

In the near future we can expect to see the introduction of several compounds similar to metronidazole. In correct dosages, I believe some will be found effective but it is likely to prove very difficult, if not impossible, to single them out on a basis of individual merit.

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