Drug Treatment of Disease

AMOEBIASIS AND AMOEBIC DYSENTERY

BY

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As in all disorders of parasitic causation, recovery and identification of the causative parasite is essential to diagnosis. The presence of the infection can always be proved by competent examination of specimens of stool. During dysenteric attacks amoebae are swept out to the exterior in the loose stools; during intermissions cysts are passed in the formed stools. Treatment in the absence of a microscopical diagnosis is speculative; it is to be deplored in all but the most rare and exceptional case. In suspected amoebic dysentery not only must the parasite be identified but its presence must then be related to the history of the patient and his symptoms. A substantial proportion (probably about 5%) of people who have never been out of Great Britain harbour *Entamoeba histolytica* in the bowel, but disease, or symptoms, due to this infection are virtually unknown among them. These people have "amoebiasis," and they do not need specific treatment. Elsewhere in the world, particularly in the tropics, this parasite in some, but by no means the majority, of those harbouring it causes amoebic dysentery and its complications. In these areas therefore its presence must always be suspect, and should receive attention. This applies to persons returned from such areas to Great Britain, as infections in them may have been acquired overseas.

TREATMENT OF ACUTE AMOEBIC DYSENTERY

The acute clinical attack will always be effectively and rapidly stopped by the intramuscular, or subcutaneous, injection of emetine hydrochloride (sold in phials). The dose is 1 gr. (65 mg.) daily until the attack stops; injections over three to five days usually suffice for this; rarely are more needed. There is no point in continuing the emetine injections after arrest of the clinical attack. Emetine given in this way, however long continued, will rarely eradicate the primary intestinal protozoal infection. Its effect is clinical, not radical (parasitic), cure; therefore relapse of the disease is probable in the absence of additional treatment to ensure radical cure.

Though emetine is a toxic drug its potential dangers have been much exaggerated. Emetine injections should never be extended beyond a 12-day period. Patients being treated with emetine injections should *always* be confined to bed as a precaution against a possible effect of the drug on the heart. Early evidence of toxicity is a continuing rise in the pulse rate; E.C.G. changes take place; a peripheral neuritis, branny desquamation of the skin, and other signs of toxicity may develop later—but all these are temporary and rarely develop if the accepted therapeutic dosage is not exceeded. In practice the drug can be given as indicated without concern.

TREATMENT OF COMPLICATIONS

Acute Emergencies

The major complications of amoebic dysentery usually appear while clinical dysentery is not apparent. They are extra-intestinal and are acute emergencies

which, if not specifically treated, are fatal. Amoebic infection can travel from the large intestine either by embolism in the portal circulation or by direct extension to surrounding tissues. In the former, and by far the more common, event an amoebic liver abscess results. If untreated this can extend to any organ or tissue adjacent to it; commonly it invades the diaphragm and right lung; sometimes it may spread further again by embolism. In the event of direct extension from the large intestine hard tumours (amoebomata), due to the amoebic together with a secondary bacterial infection, form on or adjacent to the large intestine. These tumours commonly are mistaken for neoplasms; often they are treated surgically without their causation being appreciated.

A colostomy leaking amoeba-laden matter is followed by amoebic infection of the wound tissues, with a spreading area of cutaneous amoebiasis under the dressing. There is a similar sequel to surgical drainage of an amoebic liver abscess, in the absence of specific treatment. In a continuously incontinent patient with clinical amoebic dysentery rapidly extending cutaneous amoebiasis may develop over the buttocks and perineum. These complications after surgical interference or neglect should not occur; unfortunately they do—but are rarely publicized. Very rarely there may be other complications, in the form of amoebic abscesses after embolism to the brain or other organs.

The specific treatment of extra-intestinal foci of infection with *Entamoeba histolytica* is simple and rapidly effective. Daily intramuscular injections of 1 gr. (65 mg.) of emetine hydrochloride over a period of 12 days almost unfailingly sterilize all the extra-intestinal lesions of their amoebic infection and lead to their resolution in a dramatic manner. There should be no delay in specific treatment of extra-intestinal amoebiasis, and it must never be omitted whatever other line of treatment is followed. In its absence the amoebic colliquative necrotic process continues to extend.

Liver Abscess

For treatment of an amoebic abscess of the liver there is an alternative to emetine. This is the anti-malarial drug chloroquine. The dose is an initial one of 1 g. of the salt given orally; this is followed by 0.5 g. daily for six to eight days. Such a patient may be treated with emetine and chloroquine concurrently; there is no reason why this should not be done. Chloroquine has no action on amoebae other than those in the liver. Toxicity due to chloroquine is usually first manifest by visual defects; if they occur the drug should be stopped and they will resolve.

When the extra-intestinal amoebic infection has been cleared the persisting primary bowel infection with *E. histolytica* must not be forgotten. If neglected, a recurrence of complications is likely. Successive

amoebic liver abscesses developed in ensuing years in one patient when this elementary fact was overlooked. A full course of treatment to eradicate the primary intestinal infection therefore always must follow the satisfactory outcome of treatment of any complication of amoebiasis.

RADICAL (PARASITIC) CURE OF INTESTINAL INFECTION

Claims are made for many proprietary drugs now on the market for this purpose. They are given orally, and their action is specifically on the parasites. But in addition to this, oral treatment with certain of the antibiotic drugs (e.g., the tetracyclines, erythromycin, spiramycin, and others), themselves not amoebicidal, may be followed by disappearance of the parasitic infection. These antibiotics are believed to alter the associated intestinal bacterial flora essential to the survival of the amoebae in the large intestine. There are some antibiotics which are directly amoebicidal (e.g., fumagillin) *in vitro*, but therapeutically they have proved disappointing, and in the case of fumagillin undesirably toxic. Paromomycin ("humatin") is the most recent of the antibiotics claimed to be amoebicidal, and it is stated to be free from toxic side-effects in the advocated dosage.

E.B.I.

The most consistently effective of the directly amoebicidal drugs is emetine bismuth iodide (E.B.I.); this was brought successfully into use during the first world war. Its activity so far has not been equalled by that of any other drug yet available, and it is the basis of the treatments advocated by most British physicians. The dose is 1 gr. (65 mg.) given orally thrice daily, and it alone may be given daily over 10 days; together with other drugs similarly; or on alternate days together with other drugs over two or three weeks. E.B.I. if taken in an unprotected form will be vomited; it is therefore given in enteric-coated tablets which liberate their contents after three or four hours' digestion. Some nausea even then will be experienced; this is cerebral and due to absorption of the drug; with habituation the side-effects lessen. With E.B.I. as the basis of drug treatment, radical cure of an intestinal amoebic infection can be expected in over 90% of patients.

Among the older directly amoebicidal drugs are a variety of arsenicals (e.g., "milibis") and iodo-oxyquinolines (e.g., "embequin"). Any of these when given alone is unsatisfactory, in that it will not sterilize the intestinal amoebic infection consistently and in a satisfactory proportion of cases. If used at all, these drugs should be given concurrently with E.B.I. as a supplement to it; profitably they can be given orally on alternating days with E.B.I. over a period of three weeks, so lessening the digestive upset caused by the E.B.I. Chiniofon, a water-soluble (4%) iodo-hydroxy-quinoline, can with benefit be given as a retention enema on days alternating with E.B.I. treatment, and after an enema clearance of the bowel. Its action is both directly amoebicidal and antibacterial; it is not absorbed to a material extent and is non-irritant; it promotes cleansing and healing of gross lesions in the large bowel. The arsenical drugs must be used with caution, and be stopped promptly on the appearance of any skin rash. This is rare, but if the drug is continued thereafter serious toxicity with an exfoliative dermatitis and liver damage may attend their use.

The newer amoebicidal drugs include a series of phenanthrolines (e.g., "entobex"), dichloroacetamides (e.g., "mebinol," "entamide"), and diethylaminocresols ("camoform"). All these are given orally. Reported trials leave the impression that no drug of these series has been proved the equal of, much less superior to, E.B.I. in ensuring a consistently high rate of radical cure of the intestinal amoebic infection. They have merit in their being free of toxic side-effects.

Antibiotics

Many antibiotics when given orally alter the constitution of the intestinal flora, and may consequently lead to the disappearance of an intestinal *E. histolytica* infection. The tetracycline antibiotics are good examples of these, and given alone—oxytetracycline ("terramycin") or chlortetracycline ("aureomycin") 0.5 g. 6 hourly for 10 days—will be followed by disappearance of the parasitic infection in about 60% of patients so treated. But this achievement is equalled by that of most of the amoebicides mentioned, and is much surpassed by that obtained by E.B.I. treatment. Needless antibiotic treatment in general is to be deplored, and so in this condition it is better avoided. Where the antibiotics do play a most valuable role is in those extremely rare cases which prove refractory to sterilization by repeated treatment with E.B.I. in conjunction with other amoebicides. Repetition of such amoebicidal drug treatment together with the administration of a tetracycline antibiotic has most effectively cleared these rare and unusual cases.

Harmful Treatment

Finally, and emphatically, long-continued drug treatment, whether sustained or intermittent, for "amoebic dysentery"—usually unsubstantiated by microscopical diagnosis—is unjustified. The infection is readily eradicable by a short intensive course of treatment. Indefinite prolongation of this can do no more, and it is harmful to the patient both physically and psychologically.

"Denman's pupil and son-in-law was Sir Richard Croft. He was the man in charge of the confinement of Princess Charlotte. A full account of this was the subject of Sir Eardley Holland's William Meredith Fletcher Shaw Memorial Lecture in 1951, and was based upon Sir Richard Croft's full notes of the case which had only recently been discovered by Croft's great-great-grandson, Major Richard Croft. Princess Charlotte of Wales was the only legitimate grandchild of George III, in spite of the fact that he had seven sons and five daughters. She was married to Prince Leopold of Belgium, and on her and her alone the future of the monarchy depended. The unfortunate Princess had a long labour of 54 hours, 24 of which were occupied by the second stage, and the head was on the perineum for five or six hours. Nothing whatever was done to assist delivery, and the baby—a boy—was eventually delivered without assistance. It had been dead for some hours. Charlotte died about five hours after the birth of the baby from post-partum haemorrhage. Croft never got over the shock, and shot himself three months later. Holland blames the ultra-conservative teaching of the time widely accepted as a result of Denman's writings; for example, 'Denman's Law' laid down that the head must be on the perineum for six hours before forceps should be applied. The death of Princess Charlotte changed obstetric teaching, and marked the end of the ultra-conservatism of Hunter, Denman, and Croft." (*Proceedings of the West London Medico-Chirurgical Society, 1958, Presidential Address, October, 1958, by Mr. Arnold Walker.*)