1-1-1943

Endameba histolytica and its effects of man

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and

ITS EFFECTS ON MAN

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Senior Thesis

Presented to the College of Medicine,

University of Nebraska,

Omaha, 1943.

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I

A PUBLIC HEALTH PROBLEM

Among the so called tropical diseases we find that conglomeration of pathology, signs, and symptoms caused by Endameba histolytica. For decades this parasite has been considered endemic in tropical countries, and was known to be in the temperate zones. This last fact was engraved on the consciousness of the medical men and the public in this country by the epidemic of amebic dysentery arising at the Chicago World's Fair in 1933. Since then we have taken cognizance of the fact that amebiasis is a public health problem. That it will become a much more important problem when the service men of our nation return from duty in all parts of the world is inescapable. In order to consider amebiasis as a public health problem it is "necessary to prove that Endameba histolytica is a pathogenic parasite, and that it is present in a significant proportion of the population." (23)

Before considering its pathogenicity, let us discuss the various methods by which Endameba histolytica reproduces. In 1911 Craig listed four methods: (1) simple division by mitosis, producing two cells equal in nucleoplasm and cytoplasm; (2) budding or gemmation; (3) sporulation to form multiple

small round bodies; and (4) conjugation by lying in contact so that their protoplasm streams together and separates with some interchange. (22) Another form of reproduction was described by Ivanic. He concluded that there was a process of intracellular multiplication by multiple segmentation in the tissues, but his evidence for the organism being Endameba histolytica is not conclusive. (51)

The most important method of reproduction is that of encystment. The vegetative form or the trophozoite of Endameba histolytica can live for more than a few hours in only the gut or tissues of warm blooded animals. As long as they are in the tissues they multiply by fission. In the lumen of the gut they may multiply similarly, but if living conditions become adverse for them, they form cysts. The cysts are then passed in the feces to be spread around in such manner that they may be ingested and infect another individual. This parasite needs no intermediary host in which to go through part of its life cycle. However, it may pass through a cat or a dog in a manner identical with its cycle in man. When the cyst is ingested, it again is in a favorable medium for living. Excystment occurs, usually in the colon, but maybe in the lower ileum. It is then in a pathological form and does its damage.

There has been some argument about the requisites for the maturation and rupture of the cyst. Under usual conditions the

cyst matures at outdoor temperatures. However, Yorke and Adams showed that cooling is not necessary for maturation, but cysts can develop in five hours at 57° C. Neither does cooling to 3° C. hinder their development. (97) "Excystation has been carefully studied and it has been found that a single quadrinucleate ameba escapes from each cyst through a minute perforation in its wall." (35) This undergoes a complicated series of divisions to produce eight uninucleate trophic amebae. No signs of excystation were found after two and one-half hours in the stomach, but occurred in the small intestine before three hours had passed. (48)

Many experiments have been performed to test the pathogenicity of Endameba histolytica in cats and dogs. The concensus of opinion is that ingestion of cysts is the necessary factor, but that trophozoites may be infectious if introduced per rectum. (31) Meleney and Frye state that "observations seem to indicate that strains of Endameba histolytica from different localities may show differences in the incidence of infection and in the amount of pathology produced in experimental animals." (66) However, Kessel concludes from his experimental work "that the resistance of the host is a more important factor in the production of clinical amebiasis than differences in the virulence of the parasite." (56) He is supported by Craig who concludes from his experience with troops in the

Philippine Islands that the pathogenicity of an infection probably depends on the resistance of the man. Men who were carriers of Endameba histolytica were healthy when on post duty, but when out campaigning they frequently developed dysentery. If brought to the States, these men improved considerably. (23)

Although experiments on infecting man with Endameba histolytica are rather rare, some have been performed. Craig tells of the series of experimental infection of prisoners in Manila in 1913. Twenty convicts were fed cysts from healthy carriers and eighteen of them became infected. However, only 22% of them showed signs of dysentery in an average of 65 days. Endameba coli cysts were fed to others, none of whom showed any symptoms. (23) Westphal reports an experiment in which a known carrier and a control were fed Endameba histolytica cysts along with bacteria isolated from the stools of a case of acute amebic dysentery. The carrier developed diarrhea in three days, and on the twenty-third day experienced an attack of acute amebic dysentery. The control suffered from diarrhea on the tenth day, but had no dysentery. The author suggests that a certain bacterial background may be necessary to render Endameba histolytica pathological. (93)

There have been two accidental experiments in the pathogenicity of Endameba histolytica on man. The epidemic that

started in two Chicago hotels in 1933 clearly demonstrates that Endameba histolytica can cause dysentery. In 1934 there was a large fire in the Chicago stockyards. During this fire unpurified water was drunk by firemen and onlookers. Of the 300 firemen involved, 124 became infected, but none developed dysentery. Of the 7,500 onlookers, 3,100 were infected, of whom six developed dysentery. The ratio of infection was nearly the same as demonstrated in the 1933 epidemic, but there was much less dysentery. These experiences suggest that the possibilities of developing dysentery are directly proportional to the length of the period of exposure.

In evaluating statistics on the incidence of Endameba histolytica one must take into consideration the number of stool examinations done on each person and the methods used. By a single unstained smear examination it is estimated that one-third of the cases will be uncovered. If three such examinations are made on succeeding days nearly two-thirds of the cases will be found. Further accuracy can be attained by concentration and culture methods.

Boeck and Stiles made a thorough survey of 8,029 persons of different classes all over the United States. Averaging 1.6 examinations per person, they found 4.1% infected with Endameba histolytica. From this they estimated that 10% of the population of the United States was infected. However,

the distribution of the parasite was uneven. The District of Columbia headed the list with 45% of the cases uncovered. Mississippi and New York followed with 8% and 6% respectively. Other authors have obtained similar results. Among 1060 persons examined at the University of Pennsylvania 4.1% were found infected with Endameba histolytica and the authors made the estimate of 10% if better methods had been used. (92) In Oklahoma City an infection rate of 6.8% was found. (16) A survey of men in the Navy showed on the average 11.6% were infected. It was also found that in every 1000 carriers there were 4.6 cases of amebic dysentery. (81) Another survey indicated that in certain localities the infection rate was much higher. In parts of Tennessee 40% of the population were found infected. (4) Craig compiled figures from 18 authors who found an average of 11.6% infected in the 49,336 persons studied. (23) This indicates that amebiasis is truly a public health problem, since over 12,000,000 individuals in the United States harbor the parasite.

Amebic dysentery is almost entirely an endemic disease. Very few epidemics have been reported. The reason is that seldom does the ratio of virulence to resistance become high enough in a large number of people. It has been shown that virulence does not depend on the strain of Endameba histolytica but on the numbers of cysts ingested. Resistance depends on

several factors which will be discussed later. Craig reports an epidemic that occurred among troops stationed at El Paso, Texas, in 1916. The height of the epidemic occurred from September 7 to 14 when the flies were most numerous--thus carrying greater numbers of cysts to the men. (23) The only other epidemic in this country occurred in Chicago when the victims were given large and repeated doses of cysts due to "cross connections of serious character between water and sewer lines." (18)

Because the vegetative form of Endameba histolytica is killed when it reaches the stomach, patients in the acute stage of the disease cannot pass on the disease. Therefore, we need to watch only carriers of the disease and dispose of their cyst laden stools in a safe manner. In most cities today there is an adequate sewer system that carries away the contaminated material. In smaller communities and on farms where feces are often exposed to flies special care must be taken in disposing of feces. First, and above all, human feces should never be used for fertilizing crops of any kind, particularly truck garden products. Secondly, an attempt must be made to kill all of the cysts. This can be accomplished by mixing the feces to liquid consistency with cresol 1:200 and letting it stand for at least fifteen minutes. (23)

The importance of the cyst in spreading Endameba histolytica

has caused much experimentation on its viability. Two methods are used in determining whether or not a cyst is capable of maturing: staining yellow with eosin indicates that the cyst is dead; and culturing the cysts, which is the more accurate method. (23) Craig lists the following methods of killing cysts with the time needed for each, tested by the culture method:

Left in feces	9 days
Water at 20-25° C.	10 days
Water at 0° C.	17 days
Water at 50° C.	5 minutes
Mercuric chloride 1:2500	30 minutes
Phenol 1%	30 minutes
Lysol 1%	30 minutes
Formalin 0.5%	30 minutes
Chlorine 0.01%	30 minutes

The author states that this concentration of chlorine is much stronger than can be used for water purification. Another point he makes is that cysts are killed immediately by drying and, for that reason, cannot be spread by dust. (23) Yorke and Adams got similar figures and found that the following would not kill the cysts in thirty minutes:

Mercuric chloride	1:12,500
Potassium permanganate	1.0%
Formalin	0.2%
Phenol	0.5%
Lysol	0.5%
Yatren	5.0%
Emetine	5.0% (96)

Stone found that cysts of Endameba histolytica are no more resistant to free chlorine than are colon bacteria. (88)

Evidence of previous authors outweighs his. Boeck experimented with cysts that had been ingested by flies. He found that half of the cysts were dead in 15 hours and all in 49 hours. However, if the fly happened to be drowned, half of the cysts lived for three days, but all were dead after seven days. (10) This work emphasized the importance of flies as vectors of the cysts in spreading Endameba histolytica, and the value of screening as a preventive measure.

Other prophylactic procedures are:

1. Sterilization of water. Most city systems are satisfactory because of their efficient filtration. Smaller sources must be treated by boiling, because chemicals will not work.
2. Education of the public. They should be impressed with the fact that amebiasis is common and may be dangerous; they should be informed of the methods of transmission; they should be taught the rules of personal hygiene, the most simple and important of which is a "thorough cleansing of the hands before meals and after the use of the toilet." (23)
3. Handling of carriers. It is impossible to detect all the carriers in the United States because of the expense involved. If they were found there

would be no way to compel them to take treatment. However, all food-handlers ought to be instructed in personal hygiene. They should have several stool examinations by a competent laboratory and, if found positive, should be dismissed pending completion of treatment. (23)

Natural resistance or immunity to infection with Endameba histolytica must be present to a certain extent, because many people who are definitely known to have swallowed cysts do not become infected. Musgrave believes that this fact is born out by the fact that there is a low incidence of infection in children even though they are more exposed than adults, because of their tendency to put everything into their mouths. (69) Whereas Culbertson holds that this is probably due to non-exposure. (27) However that may be, there are several factors to consider under natural immunity:

1. Age. Up to five years of age the incidence of infection is practically nil. Thereafter it rapidly rises to middle age and then slowly falls off. (65) Boeck and Stiles give the incidence between 5 and 19 as 17.6% and from 20 to 100 as 10.7%. (10) Culbertson thinks that the lower incidence above 35 is due to a comparative resistance gained from prior

infection. (27)

2. Sex. Culbertson and Craig agree that males are infected more often than females. They also state that liver abscesses are a rare occurrence in the female. (27) (23) However, a national survey showed that females were infected in 5.4% of the cases, whereas males were only 4% infected. (10) One can see that these figures do not agree with the national statistics.

3. Race. In this country there is no significant difference in the proportion of Negro and white people infected, if environmental conditions are the same. (65) In other countries white races seem to be much more subject to infection with Endameba histolytica even though their nutrition and general health are better than that of the natives. This is probably explained on a racial basis, but may be due to acquired immunity. (27)

4. Climate. Per se, this probably has no effect. However, a lowered resistance due to added strain of physical abuses and enervating weather may influence resistance. There is also more chance for heavier infection due to poor personal hygiene and inadequate sewage disposal. (27) "It seems

probable that the habits of the people, as influenced by their physiographic environment, have an influence upon the incidence of Endameba histolytica . . . . ." (65)

5. Diet. Deficiency in diet increases the incidence of infection in dogs when they are fed cysts. (27) The effect of an inadequate diet in humans is shown by a study made in two communities in Tennessee. In Hatchie acute amebic dysentery was common, whereas in New Hope it was very rare, although 40% of both communities harbored Endameba histolytica. Hatchie contained both Negroes and whites, New Hope only whites. "The following conclusions seem to be justified as a result of this study: That the diets in New Hope were more adequate in calories and vitamins than those of either white or Negro households in Hatchie." (4) Another factor that may be important is gastric acidity. In rat experiments it was found that high acidity reduced the rate of infection, by destroying the parasite. The rate could be increased by neutralizing the stomach acidity by the addition of alkali. (27)

That some degree of acquired immunity results from an

infection is demonstrated by the complement fixation test for Endameba histolytica. By using lipoid antigens extracted from Endameba histolytica a "positive complement fixation in amebic dysentery occurred in nearly 100% of the cases." (83) This represents a humoral, not a tissue immunity, and can be produced by injection of dead amebae into a rabbit. (83) However, this immunity cannot be transferred in a serum to give a passive immunity to another animal. It depends upon the presence of the amebae as a latent or active infection, and it becomes negative a few days or weeks after cure is effected.

In the preceding pages we have given a small part of the existing evidence for the pathogenicity of Endameba histolytica. We have indicated its incidence in this country, and we have made suggestions as to some of the procedures that would help control the parasite. In these war days we need to realize that several factors are likely to raise the incidence of infection and symptoms in this country. First, many of our service men are abroad and may return with heavy infections. Secondly, more people are travelling from one end of the country to the other, making for a greater spread by carriers. Thirdly, the viscissitudes of war reduce the natural resistance of individuals by increasing physical and mental strain and by reducing their already inadequate diets. Therefore, it behooves us, as medical men, to become acquainted with this parasite

and with the multitude of symptoms it may produce. These two topics will be discussed in the remaining sections.

II

ENDAMEBA HISTOLYTICA (SCHAUDINN, 1903)

This name refers to a collective species which "comprises a number of distinct races, strains, or pure lines, distinguishable from one another by the size of the cysts which they produce." (33) The development of our knowledge about this parasite began in 1860 when Lamble of Prague first reported an ameba in the feces of a child suffering with diarrhea. He was suspicious but made no definite statement about its pathogenicity. In 1875 Loesch gave a really accurate account of the organism and was able to produce dysentery in a dog with it. Kartulis in 1886 was the man who finally established the etiology of amebic dysentery as Endameba histolytica. However, it was Schaudinn in 1903 who first clearly differentiated the pathogenic Endameba histolytica from the non-pathogenic Endameba coli. As other heroes of medical research have done, he used his body on which to experiment and showed that one ameba was pathogenic and that the other was not. He died four years later of an abscess on the sigmoid flexure, having sacrificed his life for the sake of humanity. (22)

In studying this organism, two general methods are used: examination of a smear from the stool specimen with or without

a stain; and culturing a portion of the stool. In order to obtain the living ameba on a smear it is best to give the patient a saline cathartic to thoroughly wash the gut wall. Then a drop of the feces, preferably from blood or mucus, is mixed with saline for the smear. A warm stage is not necessary. The trophozoite may measure from 15 to 80 micra but they average between twenty and twenty-five micra. When at rest they are spherical in shape and resemble a white blood cell. However, they are usually moving so their shape changes. The cytoplasm can be divided into the colorless, refractile ectoplasm and the light grayish-green and granular endoplasm. In the latter, one may find crystals, bacteria, and red blood cells. (22) Heathman has reported finding red blood cells in Flabellula citata which is a free living ameba. (47) However that may be, the presence of several red cells in the cytoplasm of an ameba is sufficient evidence to call it Endameba histolytica. (23) The nucleus is rather hard to see. It is usually eccentrically placed and about five micra in diameter. The chromatin material is scarce and forms a delicate ring of refractile granules along the nuclear membrane. One of the chief diagnostic features is the motility of the trophozoites, which lasts from two to six hours at room temperature. At first it is rapid and continuous in one direction, giving a slug-like appearance to the ameba. The hyaline ectoplasm can be seen leading the rest

of the organism. This motility contrasts markedly with that of Endameba coli which moves slowly and with no apparent goal. For visualization of Endameba histolytica in the motile form the addition of neutral red 1:10,000 is very helpful. (22) (23)

For methods of fixing and staining specimens of the trophozoite of Endameba histolytica one may refer to Craig. (22, pp. 38-57) Best results are obtained by a "wet-fixing" process and the iron-hemotoxylin stain. The nucleus stains jet black with a "delicate black membrane, not over a line in thickness, the inner layer of which is covered by a layer of very minute chromatin." (23) The karyosome can be seen in the exact center, surrounded by the linen network containing no chromatin granules. The cytoplasm stains grayish, brownish, or bluish. Red blood cells can be seen and play an important part in the diagnosis. (23)

The precystic stage is the next definite stage in the life cycle of Endameba histolytica. The organism loses its motility, rids itself of ingested material, reduces in size to six or twenty micra, and becomes spherical or oval. The nucleus may be visible as a ring of refractile granules or as a refractile mass. Large refractile oval or rod-like bodies are sometimes present in the cytoplasm. The stained precystic stage is not characteristic. (23)

The unstained cyst of Endameba histolytica is a round

colorless hyaline body measuring five to twenty micra. The wall gives a double line effect. The nucleus is indistinct, but when stained with iodine it is easily visible. There may be one, two, or four nuclei. Five authors have described six and eight nuclei in Endameba histolytica cysts, but this occurrence is extremely rare. On this basis alone it is safe to differentiate Endameba coli, which may have eight or sixteen nuclei in each cyst, from Endameba histolytica, which for all practical purposes, never has more than four nuclei in each cyst. (23) The youngest cysts are uninucleate and loaded with glycogen. As development takes place chromatoid bodies make their appearance, the nuclei divide, and the glycogen decreases in amount. Later the cysts become quadrinucleate, the chromatoid bodies are well developed, but the glycogen is much less evident. (95)

In 1911 Craig wrote that "so far no satisfactory method for culturing Endameba histolytica has been found. Observers are able to grow amebae, but they do not resemble the parasite of man." (22) The first successful cultivation of Endameba histolytica was accomplished by Cutler in 1918. He used two media:

1. One egg with a few drops of blood shaken and heated and allowed to cool in culture tubes.
2. A liquid medium made by boiling one-half liter

of human blood clot with one liter of water for one hour. Then sodium chloride was added to make 0.5% solution and peptone to 1%.

He innoculated each of these culture media with five to six loopfuls of blood and mucus from a dysentery patient and incubated them at 28-30° C. It was necessary to subculture daily. (28) In 1925 Locke-egg-albumin and Locke-egg-serum media were used successfully. (11) A combination of solid and liquid media was employed by Cleveland and Collier in 1930 with a very abundant growth. "When liver infusion agar slants are covered with serum saline (1:6) and a small amount of sterile rice flour is added to each tube, it is possible to start a culture of Endameba histolytica from a single organism." (21) Deschiens found that bilirubin in cyrstalline form or in solution in the culture medium is a stimulant to growth of the organism. (32) Using Cleveland's medium, G. M. Craig found that adding Difco-tryptone and Difco-yeast extract to the medium greatly accelerated the growth of the desired organism. (26) There are now many media available for the cultivation of Endameba histolytica, and one should have little difficulty in obtaining and maintaining a culture.

In examining a stool specimen it is often of paramount importance in the diagnosis to be able to differentiate Endameba histolytica from other amebae which may be found in feces but

never produce lesions and symptoms. The commonest ameba, Endameba coli, resembles Endameba histolytica very closely, and for that reason differentiation is difficult. In the vegetative stage Endameba coli moves slowly and indeterminately. The pseudopodia are blunt and the ectoplasm is not well separated from the endoplasm. However, the differential diagnostic importance of ectoplasmic pseudopodia is only relative and can only be used if allowance is made for the freshness or age of the material. (71) The trophozoite may be a little smaller than Endameba histolytica, measuring 20 to 30 micra. Vacuoles are always present in Endameba coli. In the precystic stage these two Endamebae are difficult to distinguish. The cysts of Endameba coli range in size from 12 to 20 micra. They contain one, two, four, or eight nuclei, which is another distinctive factor. The following are the chief differential characteristics of the two Endamebae:

	Endameba histolytica	Endameba coli
Motility	Actively progressive and directional	Sluggish not directional
Inclusions	Red blood corpuscles No bacteria	No red blood corpuscles Numerous bacteria
Nucleus	Invisible	Visible
Cyst	One to four nuclei	One to eight nuclei (23)

Endilomax nana has a world wide distribution and is a common inhabitant of the human gastro-intestinal tract. Its

trophozoite measures 5 to 15 micra, contains no red blood corpuscles, and, if found early, has motility similar to that of Endameba histolytica. Its precystic form is very refractive and oval. The cyst measures 5 to 12 micra, usually 7 to 8 micra, and staining brings out one to four nuclei. (23)

Iodameba butschlii has been found in 4 to 5% of the population and has a world wide distribution. The trophozoite measures 5 to 20 micra and shows a distinct difference between ectoplasm and endoplasm. The pseudopodia are broad and hyaline. No red blood cells can be found in the cytoplasm. Motility is slugglish but progressive. Staining shows a large nucleus. The cyst is characteristic in that it is seldom round or oval, but irregular, and contains a large glycogen mass which stains deeply with iodine. (23)

Dientameba fragilis is of little importance. Its trophozoite measures less than 10 micra, has an active and progressive motility, but degenerates rapidly. Two nuclei are visible, but the cell contains no red blood corpuscles. Cysts of the organism were reported found by one author, but no confirmation has been made. (23)

Flagellates are frequently found in the intestinal tract but Craig says, "that anyone who cannot distinguish the flagellates of the intestines from amebae should not undertake the differential diagnosis of Endameba histolytica . . ." (23)

Blastomycosis hominis has often been mistaken for Endameba histolytica, even by experienced protozoologists. They exhibit a great deal of variation, ranging between 5 and 40 micra, but usually 10 to 15 micra. They are colorless, spherical, refractile, and oval or round. They consist of a "circular mass of hyaline cytoplasm surrounded by a narrow band of cytoplasm containing refractile granules, and one or more larger round or oval masses, the nuclei." (23)

In this section a short description of Endameba histolytica is given in its motile, precystic, and cystic stages. Several methods of culturing the organism are described. A brief, but to the point, description of the commonest protozoans of the intestinal tract is given so that one may decide whether or not he is dealing with the organism that causes the pathology and symptoms discussed in the next part of this paper.

III

THE DISEASE IN MAN

> "By the clinical term 'amebiasis' is meant the invasion of the tissues of man by the pathogenic ameba, Endameba histolytica. This invasion occurs primarily through the mucous membrane of the large intestine or, much more rarely, through that of the lower portion of the ileum, and symptoms of the injection vary all the way from slight digestive disturbances to the most severe symptoms of amebic dysentery or amebic abscess of the liver or other organs . . . . By the term amebic dysentery is understood a bloody mucoid diarrhea caused by Endameba histolytica and occurring as one of the manifestations of amebiasis." (23)

Palmer in 1890 wrote,

> "The term dysentery . . . . is used to designate an inflamation of the colon and rectum, producing pain and straining at the stool, called tormina and tenesmus, with scanty, mucous and bloody discharges, usually occurring frequently, but with a moderate amount of liquid or fecal matter; and these symptoms are accompanied by more or less prostration and fever." (70)

James and Deeks call dysentery the frequent passage of stools with pain, burning, and tenesmus, but do not mention blood and mucous as a necessary factor. (55) Craig emphasizes the fact that dysentery is characteristic of serious and overwhelming infections with Endameba histolytica, but that the vast majority of those infected have no dysentery and may not even have diarrhea. They have such mild infections that their symptoms are usually attributed to some other factor and not recognized as due to this parasite. However, no one harboring

Endameba histolytica is healthy and continually constitutes a danger to himself and the public. (23)

PATHOLOGY

Westphal discusses two methods by which Endameba histolytica may produce its pathology. The action of a toxin producing necrosis was considered but no necrotic tissue can be found in the amebae. Furthermore, there is usually little, if any toxemia as evidenced by fever and malaise resulting from the infection, unless it be combined with some other organism. The action of a ferment seems the more probable pathogenesis. The amebae are found in lacunae of histolyzed cells. The histolytic ferment is secreted by the organism in its vegetative phase. If the tissue resistance is not great enough, the ameba can penetrate with the help of its active mobility. The histolytic effect may be aided by the presence of certain types of bacteria. Secondary invasion of the tissues is very frequent, especially in the tropics. (94) Craig agrees with the histolytic ferment theory on pathogenesis. (23)

The following discussion on pathology is based on descriptions by Craig (23) and Bartlett (9). The pathology of of amebic dysentery is absolutely characteristic and cannot be confused with bacillary or any other type of dysentery except that caused by Balantidium coli. The lesions are most

frequently located in the rectum and just below the ileo-cecal valve, but in severe forms the entire colon may be affected. The rectum may be free, in which case, tenesmus is absent. The longer the history of dysentery, the more generalized are the lesions.

On opening the abdomen the colon has a grayish-white appearance with areas of marked discoloration. These brownish-yellow to black spots may mark the sites of large ulcers in the muscularis but are frequently extravasations due to interference with blood supply. If there is actual gangrene, segments of the gut will be greenish-black or black. In acute dysentery the colon has a dusky-red appearance. There are frequently adhesions between the colon and other intestinal coils. If the disease has been chronic there may be marked thickening of the colon which occurs first in the submucosa but affects all the coats as time goes on. These are likely to be annular constrictions producing partial obstruction, with dilatation proximally.

The mucous membrane of the colon and rectum show the following sequence of lesions. The primary lesion consists of pin-point or larger areas of cytolysis of the mucous membrane surrounded by hyperemia and edema. The next stage is a characteristic lesion of Endameba histolytica infection. Craig describes these lesions as

> "minute, nodular areas which project slightly from the summits of the folds of mucous membranes, often containing at their apices a pin-head size opening. The mucous membrane surrounding and covering them is usually much congested and may be hemorrhagic. Upon incision of these little nodules they are found to contain a yellowish or a greenish or brownish-yellow, gelatinous, semi-fluid material, which upon microscopic examination is seen to consist of cytolyzed cellular detritus and mucus and may contain actively moving trophozoites of Endameba histolytica." (23)

From this stage ulcers develop by necrosis of the mucous membrane covering the nodular elevations. The base of the typical ulcer is surrounded by congested and hemorrhagic mucous membrane. The edges are ragged, the floor is submucosa which is covered with the gelatinous fluid. The ulcers spread laterally and downward by invasion of surrounding tissue. The smallest ulcers appear "punched out", their edges being abrupt and the floor smooth. "Some of the ulcers, because of lateral extension and long, narrow openings, resemble a button-hole and are known as 'button-hole' ulcers," which are very characteristic, since the burrowing beneath mucous membrane is never found in bacillary dysentery. (23) The ulcers vary in size from 0.5 cm. to 6 or 8 cm.

> "Typical amebic ulcerations . . . . have thickened edges, considerably raised from the surface of the mucous membrane, and much undermined. Due to the presence of necrotic tissue, the edges may present a shaggy appearance which is very characteristic. The floor of the ulcers may be rough or smooth; the older ulcers having a smooth floor while in the more recent ones the floor is covered with necrotic material, pus and blood . . . . In all advanced cases . . . . the floor is formed by the muscular

coat, while more rarely, this coat will be found perforated and the floor of the ulcer is formed by the peritoneum or the omentum." (23)

The extension of the lesions laterally interferes with blood supply to the mucous membrane and may result in sloughing of considerable areas. The slough can be found in the stool along with considerable hemorrhage. The gut then has a "buffalo-skin" appearance. The three salient features of the characteristic lesion caused by Endameba histolytica are:

1. Nodular thickening surrounding the ulcer;
2. Shaggy and thickened walls; and
3. Sinuses connecting the ulcers under the intervening mucous membrane. (23)

The microscopic pathology is also characteristic.

"In that portion of the intestine not yet invaded by the ulcerative process the submucosa is much thickened, due to edema and to infiltration by numerous lymphocytes and connective tissue cells, as well as to the engorgement of the capillaries. The nuclei of many of the cells are swollen and large numbers of them show fatty degeneration. In some places the mucous membrane is packed with lymphoid and connective tissue cells and the glandular structure may be lost or greatly compressed. The nearer the ulcerated area is approached the more extensive becomes the evidence of necrosis, the cells having lost their nuclei and the normal structure of the tissue being destroyed. Amebae are found near the edges of the ulcers, beneath their base, and lying in the crypts of Lieberkuhn or in the interglandular tissue. In these locations the amebae may be collected into nests surrounded by cytolyzed tissue, or may lie within the lymphatic spaces in rows, frequently within the veins and

> capillaries. In areas in which there is no complicating bacterial invasion there is little or no evidence of inflammatory reaction in the tissue in which the amebae lie, a very characteristic finding in amebic dysentery as contrasted with bacillary dysentery." (23)

Healing of the ulcers from the center may occur spontaneously or under treatment. If the ulcers are small, no scar tissue is formed. However, large, deep ulcers produce a dense scar that may be followed by contraction resulting in partial obstruction. In carriers a certain degree of healing accompanies the activity of the organism so that destruction and construction are balanced. However, autopsy records

> "demonstrate that not only may extensive superficial necrosis of the mucous membrane of the large intestine be present, but that definite ulceration, involving even the muscular coats of the intestine, may be present in individuals who never suffered from diarrhea or dysentery . . . ." (23)

James states that "a general invasion of the colon produces dysentery." (54) From this we conclude that the same degree of pathology does not necessarily produce the same symptoms in different individuals.

SYMPTOMS AND COURSE

The most characteristic form of amebiasis is acute amebic dysentery. It has an incubation period that is very indefinite. According to Sellards as reported by Craig, cysts begin appearing in the feces on the average of nine days after exposure, but symptoms are delayed until an average of 69 days. (23) Of the men who developed amebic dysentery in the El Paso

army camp in 1916, 36% showed symptoms in one month, 66% within two months, and 90% within three months of their arrival. (23) In the Chicago epidemic symptoms appeared, in some cases, on the fourth day. Most of the victims showed symptoms in 10 to 18 days. This short incubation is rarely found and is probably explained on the basis of tremendous dosage with cysts.

The onset of the dysentery may be sudden with mucous and blood from the beginning, or a gradually increasing diarrhea may develop into dysentery in a day or two. In the temperate zones there is usually no fever unless there is some complication. In the tropics a fever of 102°-103° F. may last for two days. Even this fever may be due to a complication. Some authors go as far as to say that an infection of the gut by Endameba histolytica alone never causes fever. Prostration is not severe in uncomplicated cases. Chills, too, are rare. The abdominal pain is often of a severe cramping nature, and may continue or abate after evacuation of the bowels. At times it is generalized but more often it is limited to the right lower quadrant. Tenderness may be distributed similarly. Anorexia is usually present and nausea with vomiting occasionally occurs. The number of bowel movements varies greatly, ranging from 6 to 40 a day and averaging 15 to 20. Tenesmus may be severe, moderate, or absent, being worse in proportion to the amount of pathology in the rectum. (23)

> "Tenesmus may occur, but it is rather the exception. This is explained by the fact that the lesions are usually most marked in the cecum and ascending colon, the rectum in the majority of cases being uninvolved, or only to a slight extent. The tenesmus in bacillary dysentery, on the other hand, occurs much more frequently, and is often severe, owing to the rectum being usually much more extensively involved." (41)

An analysis of symptoms of the 1,215 cases of dysentery reported from the Chicago epidemic of 1933, shows the frequency of various symptoms as follows:

Diarrhea	88.6%
Abdominal pain	80.7%
Blood in stool	73.2%
Mucus in stool	63.6%
Loss of weight	37.0%
Weakness	36.0%
Fever	30.9%
Tenesmus	25.3% (91)

An acute case of amebic dysentery may be completely cured, partially cured to the carrier state, or may lapse into a chronic state with alternating episodes of constipation and attacks of dysentery. Fever should not be present in chronic amebic dysentery except during the acute attacks. If present between attacks, one should suspect liver abscess, particularly if there is leucocytosis and pain over the liver. In chronic cases emaciation may become so extreme that the shape of the colon can be seen and the vertebral column palpated with ease. There is abdominal pain and tenderness most of the time, increasing with the exacerbations. The colon gradually becomes thicker as more scar tissue develops

If enough of the mucous membrane is lost in the repeated attacks, a persistent diarrhea may ensue due to a lack of absorbing surface in the colon. Anemia is slow but sure to develop. After a few weeks of the disease the red blood count is usually between 3.5 and 4.5 millions, but after a year or two it drops to 2.5 to 3.0 millions. This is evidenced by the grayish pallor to the skin and definite dyspnea on exertion. If treatment is not initiated, death may occur in a variable number of years from exhaustion, liver abscess, or intercurrent infections.

The carrier state of amebiasis is much more difficult to diagnose from symptoms. Craig states that there is no such thing as a healthy carrier, although only 65% give symptoms on careful questioning. These symptoms are "exactly those encountered in a low grade toxemia," and the patient may be so used to them that he does not notice them. However, he notices a definite improvement in his sense of being after treatment for amebiasis. (23)

> "It is this very atypicalness which should suggest amebiasis and with abdominal pain as a prominent complaint and when the symptoms are characterized by chronicity and recurrency, these features all become especially suggestive of amebiasis." (80)

Naturally, the most common symptoms of the carrier state are referable to the gastro-intestinal tract. "So

varied are the symptoms . . . . that a classification would include all gastro-intestinal symptomatology." (55) Craig, Sapero, and Bannerjee list constipation, evanescent diarrhea, colicky pains and tenderness in the lower abdomen, anorexia, slight nausea, gaseous eructations, and dyspepsia as the most common symptoms encountered. (23) (80) (8) Sapero states that a "symptom-complex simulating subacute or chronic appendicitis was the most commonly observed syndrome in this series of non-dysenteric cases of amebiasis." (80)

Some central nervous system symptoms are reported by Craig. These are neuralgic pains in abdomen, back, or legs, and dull frontal headache. Circulatory symptoms such as arrhythmias, vaso-motor disturbances, flushing, and excessive perspiration of hands and feet are found. (23) Solarino reports that variations from normal in the blood picture, including red cell count, hemoglobin and color index, are very slight. (87) Castellani describes three clinical signs that may be useful in the diagnosis of amebiasis without dysentery. He concludes that they are probably due to the liver being more or less affected.

1. Infraxyphoid tenderness in 15%.
2. Dullness on the point of intersection between the right midaxillary line and a line 4 cm. below the nipple or at the

level of the sixth rib or interspace in 20%.

3. Dullness at the right base of the lung due to addensation of the lung caused by pressure of the swollen liver in 12%. (17)

It is obvious that clinical diagnosis of non-dysenteric amebiasis is rather difficult.

COMPLICATIONS

The most frequent complication of infection with Endameba histolytica is the development of one or more liver abscesses. In fatal dysentery cases at least one abscess was found in 15 to 55%. However, the average in amebiasis is very low. Predisposing factors are alcoholism, exposure, improper diet, mental anxiety, and trauma over the liver. A history of dysentery can be elicited from 75 to 90% of the patients with liver abscesses. At autopsy 97% of fatal liver abscesses show scarring of the colon. The development of the abscess usually occurs 30 to 90 days after the onset of dysentery, but may take place 6 to 12 months later. (23) The pathogenesis of this complication is that living trophozoites of Endameba histolytica are carried to the liver by the portal vein, by direct extension through the peritoneal cavity, or by the lymphatics. The proteolytic ferment acts rapidly on the liver

cells and forms a cavity containing a semi-fluid, chocolate colored mass with shreds of necrotic tissue and blood, leukocytes being rarely found. However, if secondary infection arises, the material may be purulent and full of leukocytes. The wall of the abscess shows caseation necrosis with infiltration of lymphocytic cells. Later connective tissue develops and becomes thicker to form a firm wall. (22)

Symptoms of hepatic abscess are important, because their recognition allows early treatment with an improved prognosis. In acute cases there may be a fever that irregularly rises to 102° or 103° F., and drops with chills and sweating. The liver is enlarged and tender. There may be pain over the liver, epigastrium, axilla, scapula, right shoulder, or even in the inguinal region. There is a leukocytosis that averages 18 to 20 thousand, being 80 to 90% polymorphs. If there is secondary infection, the white count may rise to 30,000. In chronic cases there is a low gradual fever, with less tenderness of the liver, and less leukocytosis. On examination a bulging over some part of the liver, with increased tenderness at this point may be found. Breathing is usually restricted on the right side, accompanied by some rigidity. Percussion shows an enlarged liver with the extension usually upward. There may be some crepitant rales and a pleural friction rub due to irritation. (23) Elliot says the "most constant

symptoms are pain in the region of the liver, loss of weight, and leukocytosis." (37)

Diagnosis of amebic abscess of the liver depends, then, on:

1. Enlargement of the liver, usually upward, and bulging or edema of the surrounding skin, with tenderness.
2. A coated tongue and an icteric tinge to the skin.
3. Leukocytosis and a fever that is irregular at first, but becomes quotidien, with profuse sweating as the temperature falls.
4. The presence of Endameba histolytica in the stools or abscess contents.
5. Response to emetine therapy.

Amebic abscess must be differentiated from infections of the liver such as syphilis and tuberculosis; from tumors, from pyemic abscesses, from other parasitic infestations such as coccidiosis, hydatidosis and schistosomiasis, from gall bladder trouble, and from estivo-autumnal malaria. (23)

A group of Chinese authors have used a radiological technique to visualize amebic abscesses. After aspiration of the cavity they inject air and 10 to 20 cc. of lipiodol. Repeated radiological examinations were used to follow the

healing process after emetine had been given for 7 to 10 days in 0.06 gram doses. At first the cavity actually became larger due to liquefaction of the necrotic wall. Gradually healing took place. Depending on the size of the abscess the time required was weeks or months. Absorption of the lipiodol took 12 months in some cases. (20)

A complication of amebic abscess of the liver is that of rupture. In a study of 604 cases, Craig found 190 that ruptured. Frequently they opened to the exterior of the body, but 70 ruptured into the pleural spaces, 47 into the lung, and 37 into the pericardium. Others connected with the stomach, lumbar region, colon, and vena cava. Any of these extensions make the prognosis more critical. (23)

Amebic abscess of the lung is seldom primary, although amebae may be carried there through the blood stream. Usually lung abscess is secondary to liver abscess. The symptoms are similar to tuberculosis. There is a daily remittent or intermittent fever with chills and sweating. The cough is constant and severe with an increasing amount of "anchovy sauce" sputum that has little or no odor, and shows blood and trophozoites on microscopic examination. There is usually some degree of pain in the chest. Physical examination shows dullness over the area, lessened breath sounds, and bubbling rales. Loss of weight and anemia may also be predominant

signs. (23)

Several other sites for amebic abscesses have been described in the literature. The brain, spleen, kidney, ovary, testicle and other organs have been infected. Abscess of the brain has been reported in 52 cases (1934). This complication never occurs unless there have been dysenteric symptoms with a previous hepatic or lung abscess. Symptoms are similar to that of any brain abscess: severe headache, nausea and vomiting, convulsions, delerium, hallucinations, and localizing symptoms. Death usually occurs in 5 to 10 days, and treatment is heroic and usually unsuccessful. (23)

Runyan and Herrick described four cases of amebic tumors of the colon which caused them much confusion. The first case encountered gave no gastro-intestinal symptoms and was thought to be a kidney tumor. The second case was diagnosed as cancer of the cecum. Their diagnostic acumen increased and they made the correct diagnosis on the last two cases. These tumors are usually large and may easily give rise to obstructive symptoms. Treatment is surgical, preceded by a course of emetine. (78) Another gastro-intestinal complication is that of amebic appendicitis which resembles the ordinary chronic appendicitis. There is slight leukocytosis and fever, some rigidity and tenderness. Symptoms are greatly alleviated by a course of emetine. (23) Peritonitis may

occur in two forms. The localized type is rather common with formation of fibrinous adhesions. Generalized peritonitis from frank perforation is rare in comparison to the number of persons infected with the ameba. The perforation usually occurs in the cecum or sigmoido-rectal region. Frank hemorrhage from the colon is rather uncommon and rarely fatal. (23)

Skin lesions caused by Endameba histolytica usually appear on the perineum, around the wound for draining liver abscesses, or around a colostomy. Heimburger found only five cases mentioned in the literature up to 1925 all of which followed liver abscess drainage. (49) Engman ascribes the following characteristics to amebiasis of the skin.

> "1. A rapidly spreading ulcerative process, the activity of which varies in different portions of the margin.
> 2. A border that presents as a whole an irregular outline as a result of the varying rapidity of progress.
> 3. An overhanging edge of dying epidermis from under which pus can be expressed.
> 4. An advancing halo beyond the margin of the ulcer which varies in color from a dusky red of various shades until it merges gradually with the color of the skin.
> 5. Pain and extreme tenderness on pressure.
> 6. The floor of the ulcer composed of indolent granulation tissue covered irregularly with debris and pus." (38)

One case of amebiasis of the penis is recorded, in a Chinese farmer. Amebae were found in the ulcer but no history of dysentery could be elicited, nor could any form of the ameba be found in the feces. However, the wife could not be checked.

Emetine gave a speedy cure. (84) Manson-Bahr mentions five skin lesions that must be differentiated from amebiasis.

1. Ulcerating granuloma of the pudenda can be eliminated by odor and venereal history.
2. Syphilitic gumma is ruled out by serology and response to arsenicals or potassium iodide.
3. Actinomycosis gives a chronic history and shows sulfur granules.
4. Tuberculosis of the skin which has a peculiar discoloration with hyperplasia and is rarely found in the perineum. It is distinguished by biopsy.
5. Post-operative synergistic gangrene has an adherent slough with no undermining.

DIAGNOSIS AND DIFFERENTIAL

Although clinical signs and symptoms are valuable, especially in cases of acute and chronic dysentery, the final diagnosis of amebic dysentery rests on the demonstration of Endameba histolytica in one of its stages in the feces, exudates, or tissues of the patient. (23) In cases with acute dysentery the trophozoite is sought. Cysts are looked for in carriers and in chronic cases between acute attacks. Three laboratory methods can be used:

1. Examination of the feces.

2. Concentration before examination.

3. Culturing a portion of the stool.

Tsuchiya favored the last method because it is comparatively simple, gives a rapid diagnosis (24 hours), abolishes the necessity of tedious repeated stool examinations, and is highly accurate. He believed that experience with a culture method was more important than the culture medium used. He used "Dorsett's egg slant covered with nutrient broth (pH 7) to which is added a heaping 4 mm. loopful of a sterile mixture of rice starch and animal charcoal in a proportion of 3:1 by volume." (90) His results comparing the three laboratory methods were as follows:

	Number of cases	Micro-scopic	Concen-tration	Culture
Acute amebic dysentery	14	14	14	13
Chronic amebiasis	86	72	77	84
Clinical cases	15	12	13	15
Carriers	71	60	64	69
Many cysts	50	49	50	49
Few cysts	21	11	14	20
Total	100	86	91	97 (90)

From this table we see that culture methods are more accurate, especially in carrier cases in which diagnosis is most difficult.

Another laboratory procedure that is being investigated thoroughly is a complement-fixation test which can be used in detecting carriers when cysts of Endameba histolytica cannot be found. It can also be used in evaluating the cure, since it

becomes negative within a few days or weeks of complete freedom from the parasite. (23) (67) Several authors are very enthusiastic about their results, claiming a high percentage of correlation between serology and fecal findings. Furthermore any strain of Endameba histolytica can be used for making the antigen, and the test is not positive with other intestinal protozoa. (23) (24) (68) (83) However, other authors find that there is considerable discrepancy between serological and microscopical findings and are doubtful as to the value of the complement-fixation test in ruling out amebiasis before an improved antigen is developed. (61) (89) Aoki reports an extract of Endameba histolytica culture that gives a positive skin reaction in all cases of amebic dysentery, and usually in cyst passers. It is negative in bacillary dysentery, typhoid and other intestinal diseases. (7)

The differential diagnosis between amebic dysentery and bacillary dysentery can usually be made on a clinical basis, but final proof again rests on the laboratory. Some cases of mild bacillary dysentery are difficult to distinguish from the more severe amebic cases. Conversely, some of the severe gangrenous amebic dysenteries give symptoms of toxemia that resemble the bacillary form. It is very possible that a combination of infections may be responsible for that state. The following is a table of diagnostic differences between

amebic and bacillary dysenteries:

	"Amebic Dysentery	Bacillary Dysentery
1.	Usually a chronic endemic disease. (May occur in epidemics)	Usually an acute epidemic disease (May be endemic).
2.	Incubation period uncertain. From a few days to months or years.	Incubation period a week or less.
3.	Onset slow and insidious but may be acute. History of poor health previously.	Onset acute. Good health previously.
4.	Course usually chronic with acute exacerbations. Fever rare.	Course usually a few days but may be chronic. Fever 102°-103° F.
5.	Liver abscess a frequent complication.	Liver abscess does not occur.
6.	Physical signs, local thickening and tenderness over ascending, transverse colon, cecum or sigmoid flexure.	Arthritis a frequent complication. General abdominal tenderness without thickening of gut.
7.	Tenesmus usually moderate in character.	Tenesmus usually very severe.
8.	Death due to exhaustion, liver abscess, intestinal hemorrhage or peritonitis due to perforation of amebic ulcer.	Death due to toxemia and exhaustion."

(23, p. 173)

In the laboratory several methods can be used to differentiate these two dysenteries. Examinations of hanging drop for trophozoites may be profitable. An attempt to culture the ameba or the bacillus should be made. Callender champions a singular method of laboratory differentiation which requires only microscope, slides, stain and a comparatively inexperienced man. He claims that a presumptive diagnosis of bacillary dysentery can be made from examining a smear of the exudate found in the stool with greater than 90% accuracy; in fact,

with greater accuracy than by standard bacteriological methods. (14) The amebic exudate contains very few pus cells, and of these 60 to 90% consist of nothing more than nuclei, called "pyknotic bodies." The red blood cells are clumped together, and Charcot-Leyden crystals can usually be found. In the bacillary exudate there is no evidence of cytolysis, but toxic degeneration is shown by the formation of "ghost cells" consisting only of periplast and a few chromatin granules. Of the cellular elements 90% are pus cells, a few are isolated red blood cells, and macrophages resembling motionless Endameba histolytica can be seen. (15)

Balantidial dysentery is a very rare disease and can be diagnosed only by microscopic examination of the stool specimen. It is very similar pathologically and clinically to amebic dysentery. Schistosomal dysentery may be confused with these, but there are the symptoms of previous migration such as remittent fever, urticaria, and dyspnea. There are likely to be fistulous tracts into the perineum, buttocks or bladder, and enlargement of the liver and spleen followed by cirrhosis of these organs. (23)

Chronic mucous and ulcerative colitis must be ruled out. This can be done most conclusively by stool examination. Chronic mucous colitis usually occurs in the nervous woman with

spastic constipation. There are recurring attacks of severe colic followed by mucous in strings or casts with very little blood. The abdomen is tender and distended and there are always complaints of indigestion and abdominal distress. The symptoms of chronic ulcerative colitis are frequently indistinguishable from amebic colitis. In ulcerative colitis proctoscopic examination reveals a congested mucous membrane that bleeds easily and exudes a muco-purulent fluid, and superficial pinhead erosions that may enlarge to definite ulcerations in severe cases. On the other hand, normal appearing mucous membrane between ulcers that have raised and undermined edges, irregular and shaggy shapes, and yellow centers, depicts amebic colitis. The exudate from these ulcers show trophozoites of Endameba histolytica. (23)

Acton and Knowles list several other diagnostic problems that may arise. Internal hemorrhoids, rectal polypi, and rectal carcinomata may be discovered by digital examination or proctoscopy. Intussusception gives rise to symptoms of obstruction and the characteristic tumor. Tuberculosis enteritis produces an extremely offensive feces in which acid fast organisms can be demonstrated. By examining the feces for ova and adult forms, one can rule out ancylostomiasis, ascariasis, and giardiasis. Thrombo-embolic phenomena of malignant malaria may cause a dysentery that can be discovered by examination of

blood smears. (1)

Again we emphasize the fact that no matter how important clinical signs are in the diagnosis or differential diagnosis of amebiasis, the final proof must come in the form of a positive stool examination.

PROGNOSIS

> "The prognosis of any infection depends on four factors: (1) the extensiveness of the pathological process. (2) the associated and secondary physiological changes produced in the host. (3) the efficiency and potency of the therapeutic principle applied. (4) the vis medicatrix naturae or the healing power of nature." (50)

Craig states that in carriers every infection can be eliminated if treated properly. The danger of death without treatment is remote, but health always remains uncertain. The prognosis in amebic dysentery is usually excellent, but depends on age (being favorable in children and poor in the aged), on whether or not it is the initial attack, and on the amount of infective material ingested. Before emetine the mortality varied from 20 to 40% and in one epidemic was reported at 90%. In the Chicago epidemic, with the help of emetine, the mortality was 5%, this high figure being due to poor diagnosis and improper treatment. Such signs as a high white count, severe hemorrhage, high fever, hiccoughs, or severe toxemia are serious. Chronic cases are very difficult to cure and are apt to become debilitated, which predisposes

them to intercurrent infections.

Any of the complications greatly increase the mortality rate. Before the advent of emetine, liver abscess was treated with open drainage with mortalities of 56%, 60%, and 73%. When emetine is used with aspiration of the abscess, a 14.4% mortality rate is high. One author lost only 1.6% of 136 cases using this method. The prognosis decreases in proportion to the number of abscesses present. Lung abscess has a better prognosis than hepatic, probably due to its natural method of drainage. Brain abscess, up to now, has had a hopeless prognosis. (23)

TREATMENT

In discussing the complicated field of treatment of Endameba histolytica infection we must remember that "amebiasis in temperate climates usually does not produce such severe symptoms as to require long continued treatment with large amounts of toxic agents." (6) We should therefore choose our drug so as to make the cure less dangerous than the disease. Hummel ascribes the following characteristics of an ideal amebicide. It should:

1. Promptly and lastingly rid the host of his infection.
2. Relieve his symptoms promptly.
3. Be non-irritating to the gastro-intestinal

tract.

4. Have low toxicity, causing no damage to any tissues of the body.
5. Readily be absorbed and eliminated.
6. Destroy ameba and cysts in the lumen and tissues of the gut.
7. Be easy to administer, preferably by mouth.
8. Not interfere with the usual activity of the patient.
9. Be effective at low dosage.
10. Be reasonable in price. (50)

Three criteria should be fulfilled before making a claim for cure. These are: symptomatic relief; clinical improvement; and, consistent failure to find cysts in the stool for three months. (75)

General measures of treatment are very important in that they enhance the effectiveness of the preparation employed. Treatment of carriers can be given to an ambulatory patient, if it is economically important that he stay at work. However, he should be cautioned against any indiscretions of alcohol, diet, or exercise which might negate the treatment. The acute dysentery case should be put on complete bed rest with perhaps a little phenobarbital to reduce peristalsis. In case he is having cramping pains, paregoric may be given in

4 to 8 cc. doses every two hours. His fluid intake should be above three liters a day and his urinary specific gravity should be kept below 1.020. His diet should consist of small quantities taken every two hours. It should be low in fat, rich in vitamins, and with adequate calories. (74) Craig suggests broth and egg albumin for the first two days, followed by barley or rice water. As soon as symptoms have abated, milk, eggs, soft puddings, and semifluids may be added. Hot sauces, green vegetables, alcohol, and foods containing much sugar are to be avoided. Tonics may be given, and a change to a cool climate is helpful. (23) Ghosh thinks that one of the difficulties in effecting a cure in India is that the average diet produces a stool that is acid in reaction. He treated three chronic cases with emetine and kurchi after giving them a diet that made their stools alkaline. They were instructed to stay on a diet of high protein, low carbohydrate, and to substitute wheat for rice. Their stools remained negative for Endameba histolytica for at least 6 months after treatment. (42)

In discussing the drugs used in amebiasis we shall classify them into 4 groups:

1. Alkaloids extracted from plants.
2. Halogenated oxyquinoline derivatives.
3. Organic arsenicals.
4. Miscellaneous drugs.

Alkaloids. The most commonly used alkaloid is emetine which is obtained from the root of Psychotria ipecachuana. This drug is a protoplasmic poison and kills trophozoites of Endameba histolytica in concentrations that are non-toxic to man. It does not affect cysts in safe concentrations and, therefore, cannot be used in most cases of amebiasis. The actions of emetine on Endameba histolytica have been studied in great detail. James says,

> "I have never found a normal endameba after the third day of emetine, although I have encountered degenerating organisms as late as the seventh day . . . The appearance of endamebae after the administration of emetine suggests that the drug is a specific poison against them. The fragmentation of the nucleus and the broken up appearance of the cytoplasm are indicative of this fact." (53)

Dobell and Laidlaw say that 1% emetine is needed to kill Endameba histolytica immediately, (34) but that in a culture medium consisting of inactivated horse serum and Ringer's solution (1:8), emetine will kill the parasite in four days when diluted one part in five million, if the reaction remains alkaline. (59) St. John reports that in acid media ameba are killed by emetine concentrations of 1:1,290 in five hours, and may or may not be killed by 1:10,000 in 24 hours. In alkaline media dilutions of emetine 1:5,000,000 "regularly depressed the growth curve in two of three strains and this dilution of the drug resulted in death of amebae in three or four days." (79) Both authors agree that emetine is very

much more effective in alkaline media, which gives support to Ghosh's claim for better results with emetine when a diet producing an alkaline stool was used. St. John also states that growing Endameba histolytica in 1:400000 emetine culture with an acid reaction produced no change in its susceptibility to emetine after 47 days. (79) Other authors report that if a strain of Endameba histolytica is grown on a media with a gradually increasing concentration of emetine, this strain will become resistant to the action of the drug. One strain increased its resistance eight times, during a series of emetine cultures. (12) (45) This fact may have some bearing on the ineffectiveness of emetine in some cases that have been repeatedly treated with the drug.

The earliest form of emetine administered was the mixture of alkaloids called ipecachuana. Its use was in good repute at the turn of the century, but better and safer drugs have been developed. It is now used only as a last resort. Simon became converted to its use in 1909 after using it successfully for two years and suggests the following procedure. Salol coated tablets containing 0.325 gram of powdered ipecac are used. After a week of liquid diet and a castor oil purge, eight to ten tablets are given each evening, reducing the dose by one tablet every evening until three tablets are being given. Give three tablets every night for two weeks with

absolute bed rest and a well controlled semi-solid diet.- (86)

Since 1912 emetine in its purified state has been used with great success in the treatment of acute amebic dysentery. It is given subcutaneously or intramuscularly with equal success. Intravenous use is heartily condemned because of its increased toxicity to the patient. The dose for an adult is 0.065 gram a day for not more than 12 days. The course can be repeated after a month. In children over eight, give doses of 0.02 grams, if younger, give 0.01 gram. (23) Emetine is valuable in the treatment of acute amebic dysentery, amebic hepatitis, with or without abscess formation, amebic skin lesions, and other complications. Its use in the treatment of chronic and carrier cases should be considered an abuse. (19) Craig suggests that emetine be used in acute cases for as many days as is necessary to cure symptomatically, providing this is not more than 12, and to follow this drug with a course of chiniofon. If a chronic case is to be treated during an exacerbation, a similar routine should be used. However, one must remember that in some chronic cases the diarrhea may not be due to active lesions but to a large amount of scar tissue that prevents resorption of fluids. In this case, limiting the fluid intake may help. Emetine has no place in the treatment of a carrier. (23) James and Deeks state,

> "Emetine . . . . is a most favorable drug in the treatment of acute amebic infection, but rarely effects a complete cure unless combined with other methods of attacking the parasites. This is probably because its action, for the most part, is against the parasites in the tissues, and it does not effect a complete elimination of luminal parasites."

They suggest that bismuth subnitrate is a suitable drug for accomplishing this last feat. (55)

The value and the danger of emetine rests on its being a protoplasmic poison. Toxic effects on the patient occur rapidly if large doses are given, or slowly by accumulation with a series of smaller doses. The symptoms are usually "sudden cardiac failure, myocarditis, wrist, ankle, and toe-drop, muscular pain and weakness especially of arms and legs, severe diarrhea, nausea and vomiting, and great prostration." (23) Caution should be used whenever emetine is prescribed and a careful search for toxic symptoms should be made daily, especially if there is any hint of renal or cardiac disease. Anderson and Reed report one case that tolerated only a partial course of emetine and years later retained electrocardiographic evidence of permanent myocardial damage. (6) This case is not alone in the literature, and should serve as a warning to those who prescribe emetine indiscriminately. It is a mistake to treat amebiasis by repeated small doses of emetine; to avoid hypersensitivity, adequately large doses should be given to cure when beginning treatment. (82)

Because some of the nervous and muscular manifestations of emetine poisoning resemble polyneuritis, thiamine hydrochloride was used in doses of 10 mgm. daily in cases of emetine intolerance with excellent results. (3)

Preparations containing emetine, bismuth, and iodide (29%, 12%, 58% respectively) have been used in emetine resistant cases. Their toxicity is that of emetine. The dosage is 0.2 gram orally in a gelatine capsule once a day for 12 days. There is always nausea on the first or second night and diarrhea on the fourth, fifth, or sixth day. A course of this drug leaves the patient weak and depressed, but they regain their vitality in a few days. Bed rest should be insisted on for the treatment and for three days following, after which a program of graduated activity is initiated. Because of its danger and unpleasant effects, this drug is seldom used. (23)

Another series of amebicidal alkaloids are obtained from Holarrhenia antidysenterica or "kurchi bark". The extract is not very toxic and may be given intramuscularly in doses of 0.065 gram three times a day for as long as six weeks. Orally, 8 cc. are given with the same frequency. (23) However, the most commonly used preparation is kurchi-bismuth-iodide (27%, 23%, 50% respectively). Acton and Chopra suggest using 0.65 gram two times a day for ten days. They say there is

no cumulative effect, and the treatment can be repeated immediately if necessary. They claim it has no depressant, toxic or emetic effect. On a series of 78 chronic cases they effected a cure in 73%, failed in 23%, and were doubtful about 4%. (2) Hummel insists that neither kurchi nor any of its preparations has any place in modern therapy of amebiasis. (50)

An ancient Chinese natural remedy for dysentery was the "kosam" seed. Liu reported the treatment of 19 cases by 20 to 50 seeds a day for 15 to 20 days with an 80% benefit. The amebae disappeared from the stools in an average of 2.6 days. (60) A group of authors later stated that in vitro "kosam" seed had amebicidal effects equal to that of many known remedies, but clinical tests did not substantiate Liu's report. (58)

From this survey we conclude that emetine is the only alkaloid that has much place in the treatment of amebiasis; that it should be used only in cases with acute dysenteric symptoms or with complications; and great care should be taken to observe toxic symptoms. The recommended dose is 0.065 gram given hypodermically into subcutaneous tissue or muscle once a day for not more than 12 days in sequence.

Quinolines. The oldest and commonest quinoline derivative used in amebiasis is chiniofon or "yatren" or

"anayodin". It contains 26 to 28% iodine, and is non-toxic when given in therapeutic doses. Two deaths have been reported from its use intravenously, but when given by mouth the only symptom of intolerance is diarrhea. It acts directly on Endameba histolytica in cystic state and Craig is very enthusiastic about its use. He states he "has never been obliged to resort to any other drug in the treatment of carriers of this parasite for the past 5 years." (23) Hummel agrees that there is very little toxicity but obtained only 75% success. (50) The dosage is 1 gram three times a day for eight or ten days. Sometimes a second course is necessary. The drug can be given to ambulatory patients without precautions against over exercise or over eating. It is therefore an economic boon to the working carrier. It is safe to use in treatment of large groups of people.

Vioform is a quinoline compound containing 37 to 41% iodine and 11 to 12% chlorine. Its toxicity is very slight, but of 60 cases, one had palpitation, dyspnea, and headache, and two had excessive flatulence, nausea, and bloody mucous in the stool. (6) The dosage is 0.25 gram three times a day for ten days, the course being repeated in a week, if indicated. Girges suggests that enemas of 1 to 2% vioform totaling 200 cc. be given to chronic cases, in addition to the regular oral dosage. (44) Out of 47 cases treated orally,

one was obstinate, and 6 recurred, possibly due to their poor environment and reinfection. (29) Mayer used twice the dose and obtained a cure in all 15 cases of acute or subacute amebic dysentery, in 11 of 13 cyst passers that showed symptoms, and in 16 of 18 cyst passers that gave no symptoms. Stools were still negative after six weeks. (64) The preliminary results are encouraging but further study on clinical results are necessary before vioform can be fully accepted.

Two quinoline derivatives that have recently been used in amebiasis with excellent results are iodoform and diodoquin. The latter was used by Silverman on 25 cases, 9 of which were the acute fulminating variety. He gave 1.5 grams to 2 grams a day for a varying length of time with universally successful results. Amebae were gone from all stool specimens in 16 days and were checked for a time varying from one month to nine, with no recurrences. (85) Hummel gave doses of 2 grams a day for 20 days to 26 patients without any signs of toxicity. All amebae disappeared by the tenth day and there were no relapses in eight months. He writes that "diodoquin comes nearer fulfilling the criteria of the ideal amebicide than any other preparation available at the present time." (50) Iodoform was tried by Radna on 11 cases of dysentery and 4 cyst passers. The dosage was 0.05 gram the first day, 0.01

gram the second, 0.02 gram the third, and then 0.03 gram daily for 15 to 22 days. All stools were negative in 15 to 30 days, but one case suffered a relapse in four months, which may have been reinfection. (73)

The most effective quinoline derivative that has been thoroughly proved is chiniofon. Its use is chiefly in carriers and in acute dysentery, as a supplement to emetine. Diodoquin shows great promise, but has not been used in enough cases, as yet, to definitely prove its low toxicity and high effectiveness.

Arsenicals. Of these compounds carbarsone is the drug of choice. If an arsenical is called for, it should be carbarsone because it is the most effective against the parasite and the least toxic to the patient. The usual dose is 0.25 gram two times a day for ten days, with a repetition after ten more days, if indicated. Hummel and Sapero report that 25% of patients are not cured by this regime. (50) (80) Craig lists several series that had 90% success. (23) Other authors have used the above regime of carbarsone and at the same time given chiniofon enemas. The enema consists of 250 cc. of 2.5% chiniofon in water and is repeated every other night. It is given in the knee chest position and the patient is instructed to remain in this position for 5 minutes, to lie on his right side half an hour, on his back half an hour, and on his left

side for half an hour. With this combination of drugs the percentage of cure among 104 cases of acute, chronic and carrier cases was 97%. (63) (74) Toxicity of carbarsone is rather low, only one death being reported in the literature of its use in amebiasis. (50) In a series of 330 cases treated by full doses of carbarsone, only one had severe gastro-intestinal upset with liver damage, while two others were nauseated. In none of the cases was there any "evidence of skin, optic nerve, or renal damage from the use of carbarsone clinically." (6)

Acetarsone has been used in the treatment of carriers and mild cases of dysentery, but its effectiveness is less than that of carbarsone, and its toxicity is greater. The drug is cumulative and may produce colic, diarrhea, puffiness of the face and lids, or an erythematous eruption. It is not recommended now because safer drugs are available. The dosage required for therapy is 0.25 gram three times a day for one week, with repetition after a week's rest. Craig found that half this dosage gave the same results without the danger. This drug can be given to the ambulatory patient, but he should be closely watched for signs of toxicity. Cures up to 60% have been reported in one course, with an increase to 80% in two courses.

Treparsol has also been used in doses of 0.25 gram two

times a day for four days, with a rest of ten days between courses. Craig reports 89% cure when three courses of treparsol were used along with emetine. (23) Hummel says that this drug and "stovarsol are cumulatively toxic and may produce gastro-intestinal upset with pain and cramps, diarrhea and flatulence, and toxic dermatitis." (50) However, Brown concludes from his work that "treparsol and stovarsol are equally efficient, but since treparsol is rapidly eliminated, it would seem to be preferable to stovarsol." (13)

Among the arsenicals, carbarsone stands out as the drug of choice.

> "It is clinically non-toxic in effective doses, it may conveniently be administered orally without interference with the patients' usual routine, it has no untoward side reactions, and it is comparatively cheap." (75)

Miscellaneous. Bismuth subnitrate has been advocated by James and Deeks in the treatment of amebiasis, especially acute cases. They prescribe rest, milk diet, one to six saline irrigations of the colon daily, and huge doses of the drug. Twelve grams of bismuth subnitrate are mixed with an effervescent solution and given every three hours until the stools become less frequent and the tongue is clean. Then the dose is administered only four times a day. Of 190 cases there were only three relapses. When combined with emetine, 4.5% of 66 cases relapsed. Nevertheless, they say,

> "Bismuth subnitrate when used alone under proper conditions will bring about a cure in a large number of cases . . . . but its effect is enhanced by the simultaneous administration of emetine." (55)

Toxicity of bismuth subnitrate is sometimes shown by cyanosis due to the formation of methemoglobin. There are four fatal cases mentioned in the literature. (77) Perhaps this can be avoided without decreasing effectiveness by using bismuth subcarbonate. (6) The champions of the drug say that the cyanosis is due to an impurity in the drug and that it can be cured by administering magnesium sulfate orally. (55) The action of the drug on the ameba seems to be due to its antiseptic qualities. It kills bacteria which have helped the ameba to live. "The disintegration of endameba following bismuth is a mechanical one . . . . and is probably brought about by the inhibition of a certain necessary food supply." (53)

Other drugs that have been used are emetine peroxide, auremetine, chaparro amargoso, and di-hydranol. The first three are of questionable value and are best left alone. (23) Di-hydranol "appears to be a particularly satisfactory therapeutic for chronic and carrier cases in children as well as in adults, and for those patients where hospitalization is impossible." (39)

Treatment of Complications

The treatment of complications may be summarized by saying

that whether the abscess be in the liver, the lung, the appendix, the brain, the skin, or any other organ, the only drug of any value is emetine. (23)(49)(76) It is given hypodermically in doses of 0.065 gram a day for 12 days, followed by a rest period and another course, if necessary. The abscess should be drained, preferably by aspiration. Operation for drainage of a liver abscess is dangerous and carries a mortality, of 22%, even when used with emetine, whereas aspiration is only 9.9% fatal. In a debilitated patient with liver abscess, aspiration and administration of emetine is the only safe procedure. (5) "But it must be recognized that liver puncture in a very sick man is a considerable trauma" and it may be necessary to restore strength before attempting this procedure. (72) Aspiration is usually performed after the administration of 5 or 6 doses of emetine. If there is marked tenderness at any point, it is done there. If there are no localizing signs, the needle is inserted inwards and upwards in the eighth or ninth interspace in the anterior axillary line. Aspiration may be repeated as often as necessary. Open operation is indicated only if fluid reappears after several aspirations, secondary infection sets in, or a subphrenic abscess develops. (23)

Prophylaxis

It has been demonstrated that a permanent immunity is not

developed after infection with Endameba histolytica nor can immunity be aroused by any kind of vaccination. Passive immunity cannot be transferred. Therefore the only prophylactic measure possible is medicinal in nature. It is not feasible to continually give amebicides to persons residing in parts of the world where amebic dysentery is prevalent, because of the inherent dangers of continual medication. However, prophylaxis for persons travelling through a country with high endemic rate of infection may have some value. For this purpose, diodoquin is probably the best and safest drug available. Sufficient dosage is 1.5 grams a day for 20 days. If the stay in the region is longer, another course may be given following a week's rest. (25)

In summarizing treatment of amebiasis, we find that many types of drugs have been used. This fact, in itself, indicates that there is no proven specific for Endameba histolytica. As a general rule it is best to change drugs, rather than repeat the same one more than twice. Best results have been obtained by combination therapy, adding the effectiveness of one drug to another. In acute cases and in the complications of amebiasis, emetine has no substitute. In carriers, in chronic cases, and in the controlled stages of acute cases carbarsone or chiniofon are indicated, the latter being the less toxic of the two. Carbarsone by mouth along with chiniofon enemas has given

excellent results. Bismuth subnitrate and di-hydranol must be kept in mind. By using some drug, or combination of drugs now available, we should have no difficulty in completely curing the great majority of amebiasis.

IV

CONCLUSION

Endameba histolytica is an organism pathogenic to man. It can be found in more than 10% of the population of the United States. These facts establish amebiasis as a public health problem that will increase in importance with the world wide travel and changed living conditions necessitated by the war.

The recognition of Endameba histolytica and its differentiation from other parasites of the human gastro-intestinal tract require special training and experience. Its chief characteristics are active, progressive motility and the presence of ingested red blood cells in the trophozoite, and one to four nuclei per cyst. Routine stool exams are recommended in order to recognize more cases of amebiasis.

The pathology produced by Endameba histolytica is an ulceration of varying degree of the colon, the sigmoid, and/or the rectum. The degree of pathology does not determine the severity of the symptoms. The symptoms of acute amebic dysentery are diarrhea with blood and mucous, some tenesmus, and very little toxemia. Chronic cases have periods of fair health interspersed with exacerbations of the condition, to the acute form. Carriers may have symptoms that run the gamut

of gastro-intestinal symptomatology, or they may have none. Complications occur in the form of abscesses, most often in the liver. The final diagnosis of amebiasis rests on finding trophozoites or cysts of Endameba histolytica in the stool. Prognosis, with modern treatment, is very good. When there are dysenteric symptoms, emetine should be used in the treatment of amebiasis. Otherwise the arsenical carbarsone, or a quinoline derivative, such as chiniofon or diodoquin, is indicated. With one or more of these drugs it is possible to cure almost all cases of amebiasis.

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