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AMEBIASIS AND AMEBIC DYSENTERY

SENIOR THESIS

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DEFINITION

Entamebic Dysentery is an infectious disease of universal distribution caused by invasion of the structures of the large bowel by *Entameba Histolytica*. Anatomically, the most characteristic feature is an undermining of the submucosal layers of the large bowel. Extension of the ulcerative process takes place in the mucosa and may extend deep into the muscular and peritonea coats. The clinical course of the disease is marked by irregularity and inconstancy of symptoms, being more or less intermittent in nature. Exacerbations are usually characterized by frequent, scanty evacuations containing mucus and blood; by abdominal pain, tenesmus and general body depression, to be followed by abeyance of clinical symptoms of the early cases. Approximately onethird are cured by a single complete course of emitine, while patients who have relapses have a good outlook if the relapse is treated persistently and thoroughly.

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HISTORICAL SUMMARY

The disease has been known since the most remote periods of time as an independent malady of wide-spread and almost universal distribution. The earliest writings on medicine refer to the disease; especially in army records. The disease holds a very prominent place in historical records of practically every nation. The cause was not known, but the disease was commonly known as the bloody-flux, with a confused clinical picture and indefinite causation.

Lambl in 1859 (1) was the first to offer a suggestion as to the possible specific cause of the malady. He discovered peculiar motile organisms with ameboid movement in the stool of a child who had died of enteritis. These impressed him as a possible specific cause of the disease, but his theory was not accepted until several years later. However, his theory was further substantiated by Lewis and Cunningham in 1870 (2), who found ameboid-like organisms in the stools of cholera patients.

The credit for discovery and demonstration of the organisms seems to be granted to Losch in 1875 (3). He attracted universal attention to the possible relationship between the organism and the disease. He reported a case of a Russian who suffered from typical symptoms of acute dysentery, in which he noticed large numbers of amebae in the stool. His description corresponds almost identically with our present conceptions of the morphology of *Entamoeba histolytica*. The

patient died in four months with an inter-current pneumonia. An autopsy was performed and the large bowel was found to be extensively ulcerated. He was able to produce similar lesions in dogs by inoculating them with the scrapings of the ulcers. He inoculated four dogs of which one became infected and died, which showed almost identical findings with that of the deceased. He was also able to recover the organisms in large numbers from the dog before death. The remaining three dogs were apparently not affected. Because of this factor he was led to believe that the amebae were not the direct cause, but that a secondary invader was the cause of death. However, his findings and records stimulated much investigation on the subject of the ameba as a possible causative factor of the disease.

Grassi in 1879 (4) discovered cysts in the stools of healthy individuals as well as those suffering from the disease, and from this he concluded that the organisms were not pathogenic.

Koch (5), in 1883, was appointed to make a study of the dysenteries in Egypt by the German government. He observed motile amebae in patients suffering from dysentery, with identical morphology of that described by Losch in 1875. Kartulis (6) was impressed by Koch's findings and he made a study of over five hundred cases of dysentery in the Nile valley. He found numerous amebae in stools of these cases and from this observation was convinced of the pathogenicity of the organisms. He succeeded in reproducing the disease in kittens by inoculating them from the intestinal flora of such patients and also from abscesses of the liver. These experiments were later proven and confirmed by Hlava (7), at Prague in 1887, through a series of experiments

and observations on cats and dogs.

Osler (8), in 1890, is given the credit for being the first to discover amebae in the United States. Shortly thereafter confirmation came from various sources throughout the world. Within one year Stengel (9), found three cases of amebic dysentery in Philadelphia; Musser (10) reported four cases from the same city; Dock (11) reported twelve cases of acute and chronic forms from Galveston, which were the first to be recorded from the far South.

At this time there arose considerable discussion and debate as to the correct nomenclature of the organisms. Losch described and named it *Amebae Coli*; while Councilman and Lafleur (12) in 1891 changed it to *Amebae Dysenteria*, solely upon clinical grounds. The former term being retained, according to them, for species of non-pathogenic nature, which were believed to be present in the intestine of man and animal at this time. Quincke and Roos (13) interested themselves in the pathogenicity of the previously described organisms, using cats as the basis of their experiments. Their conclusions only added stronger confirmation to those of Councilman and Lafleur.

Schaudinn (14) in 1903 presented his series of highly important observations on the morphology of pathogenic and non-pathogenic ameboid organisms found in the stools of man, which were later confirmed by Craig (15) in 1905. He accepted the special genus *Entameba*, which had previously been described by Cassigrandi and Borgogallo (16), as a basis for classification of the parasitic amebae for man, and en-

ameba coli as the non-pathogenic amebae for man. This classification was widely accepted by workers in the field for some time. However, in his later studies Schaudinn showed that he had failed in working out the complete life cycle of *entameba histolytica*. Thus the incompleteness of his work was a basis for much subsequent confusion.

Hartmann and Viereck (17) in 1906, described a third species under the name of *entameba tetragena*. Walker (18), in 1912, and shortly thereafter several other men, were able to prove that *entameba tetragena* was not a separate species but represented a phase of the life cycle of *entameba histolytica*.

A few years later Elmissian (19) described *entameba minata* as another separate specie, but this was found to be a part of the life cycle of *histolytica*.

Wenyon (20), in 1916, discovered *entameba nana* which as yet remains a distinct type of parasitic amebae. This specie was found in many people in Egypt. This specie was later called *endolimax* by Kuenen and Swelengrebel (21), in 1917. Brug (22), in 1918, named it *endolimax nana*, the name by which it is now known. The in same year Jepps and Dobell (23) described still another ameba living in the intestine of man. They named it *Dientamedia fragilis*.

The credit for first culturing *Entameba Histolytica* was given to Cutler (24) in 1918. Boeck and Drbohlav (25) confirmed his observations and later devised a medium which they believed to be more satisfactory in culturing the organisms. Craig (26), in 1927, also devised a medium which has proven to be more satisfactory.

Since this time it has been found and demonstrated by Craig that *Entameba Histolytica* produces antibodies in those harboring the organism and he has devised a method for serological diagnosis of this form of dysentery. A similar technique is used as in the Wassermann test for syphilis. However, this test is of little practical value due to difficulty in preparing the constituents, and technic of the test.

ETIOLOGY

PREDISPOSING FACTORS: While it is generally known that the exciting cause of amebic dysentery, and other allied morbid conditions, lies in the infection with *Entamebã Histolytica*, there are undoubtedly certain factors which make the tissues more susceptible to the specific organism. The mere presence of the organism within the lumen of the intestine does not in itself imply actual tissue invasion. Conditions must be favorable for the vegetative state of the organism in each case before actual penetration of the intestinal wall is possible on a large scale. Simons (27), as well as others, has shown that some individuals show a definite degree of immunity against invasion even though the individual's intestinal tract is constantly being bombarded with pathogenic amebae.

The following causes may be considered as predisposing factors in the disease:

Strong (28) observed in the Philippines that the greater number of cases occurred during a heavy rain between June and September. Rogers (29) likewise concluded that dysentery was more prevalent in rainy seasons of the year in India and that there was a gradual cessation in the number of cases with subsidence of the rainy season of October. Heavy and prolonged rainfall favored the transmission of the infection, preserving the life cycle of the cyst, which according to Rogers succumbs readily if deprived of a liberal amount of moisture; also by washing the cysts out of the soil and stagnant pools to open up new routes of contamination and transmission of the disease.

TEMPERATURE: According to Simmons and Brown (30), the temperature seems to play a part in predisposing one to the disease. From their experiments, each working independent of the other, they concluded that the disease was more prevalent during moderate temperatures, becoming less prevalent in the hot summer months from April to May, with a steady rise beginning in the fall, extending well into November. We also see another decline during the coldest winter months.

ALTITUDE: The disease is seen most abundantly in the lower altitudes. However, this does not mean that it is not present in the higher altitudes, but merely that the exciting organism is much more easily transmitted in the lower altitudes, swampy districts, etc.

GEOGRAPHICAL DISTRIBUTION: It is a disease of universal distribution. Primarily it is more prevalent in the tropical countries; as India, Egypt, Asia Minor, Central America, South America, the Philippines, Southern China, and other tropical or sub-tropical countries.

RACIAL: All races are found to be equally susceptible to the disease. However, it is believed by authentic workers in the field that the natives of tropical countries build up a certain amount of resistance and immunity to the disease, while foreigners do not have this resistance and are most likely to contract the disease.

SEX: Males have been found to be more susceptible than females. Simons (31) out of 217 cases studied, 180 were males and only 37 were females. Fuchter (32) made a study of 119 cases and found 108 were males and 11 females. Strong (33) had 200 cases under his observation and 177 of these were males. The only possible reason for

this being that the male sex lead a more active life and occupational contacts expose them much more frequently to the organism.

AGE: The disease seems to be more prevalent in middle adult life. Simons' study of 217 cases, the youngest of which was fourteen and the oldest sixty-eight years of age. Kartulis (34), according to his observation, believed that all ages were equally susceptible, but children were not exposed to the etiological agent as frequently as the adult. DeBuys (35) found four cases out of 300 in the outdoor pediatric clinic of New Orleans. His conclusions agreed with those of Kartulis. Canata (36) examined 6,000 children between the ages of two and fifteen in one of the endemic centers of Brazil and found only 100 children to be infected. His conclusions agreed with the above. A peculiar feature worthy of mention is expressed by many of the authors; that the prognosis of dysentery in infancy is more favorable in regard to morbidity than it is in the adult, because complications are usually lacking.

OCCUPATION: This undoubtedly plays a major role in the disease. Men who are employed in heavily infected regions, and those whose occupation is apt to bring them in contact with contaminated water supply, are without question subjected to greatly increased chances of infection. The disease is found to be more prevalent among those engaged in such occupations as logging, ditching, truck farming, railroad construction, civil engineering, and other fields of work which carry individuals in contact with swampy regions. Wenyon (37) through his examination of British troops in the tropics found that 9% of the 398

chefs were infected and was able to demonstrate the organism in each case; while in contrast to this, he found that on observing the troops, only 5.3% of 1,979 were infected. He acknowledged his inability to explain this observation, unless the cause may be due to the large number of flies and insects about the cook houses of the army camps.

SANITARY CONDITIONS: Wenyon has shown that the cyst of *Entameba Histolytica* may be swallowed by flies and insects and redeposited on food and drinking water without losing its viability. Thus we see the need of safe-guarding against access of flies and insects to the kitchen and dining rooms of tropical and sub-tropical regions. Overcrowding and unsanitary conditions aid greatly in impairing the resisting forces of the host and favor the invasion of the organism. Sanitary food conditions are very essential in the prevention of the disease. Not infrequently an outbreak of the disease can be traced to the commissary departments of army camps, hotels and various eating places. Such an outbreak can be vividly traced to the Chicago epidemic of 1933.

EXCITING CAUSES: It has been definitely proven that *Entameba Histolytica* is the exciting cause of amebic dysentery. However, there are other similar parasites which may invade the intestinal tract of man, but according to observers *Entameba Histolytica* is the only one pathogenic to man. Since there are so many intestinal parasites, it might be well at this time to classify them as to their characteristic morphology.

CLASSIFICATION AND NOMENCLATURE: Parasitic amebae found in man and lower animals are protozoa, or single celled animals belonging to the class of Rhizopoda. These parasites are typical singlecelled, non-

cellular organisms, the body consisting of a mass of cytoplasm in which is found a nucleus or nuclei, ingested materials, and vacuoles. However, as before mentioned, only one species is pathogenic to man, this being *Entameba Histolytica*. Much difficulty has been encountered in attempting to classify the various species because of the small size and simple morphology, and then too, possibly to our lack of knowledge of the life cycle of the different species. We also encounter technical difficulties in staining and culturing, and differences of opinion among well trained protozoologists regarding the basis of classification. At present we have generally accepted a classification and nomenclature which may be satisfactory only for a short time or until further discoveries are made.

- Genus I. *Entamoeba* Leidy, 1879
 - Species in man
 - Entameba Histolytica* "Schaudinn, 1903". Hicon, 1909.
 - Entameba Coli* "Grassi, 1879", Smith, Middleton and Darrett, 1914.

- Genus II. *Endolimax*, Kuenen and Swellengrevel, 1917
 - Species in man
 - Endolimax Nana*--Wenyon, O'Connor 1917, Brug 1918.

- Genus III. *Iodamoeba*--Dobell 1919
 - Species in man
 - Iodamoeba Butschlii*, "Prowazek 1911", Dobell 1919.

- Genus IV. *Deintamoeba*--Jepps and Dobell, 1918
 - Species in man
 - Dientamoeba Fragilis*, Jepps and Dobell, 1918

(Note: Craig's classification (38))

Thus we see from Craig's classification that man is parasitized by six different species of the amebae belonging to four

different genera, and of these, five species have been found to be parasitic to man in the intestinal canal by some observers, but man is so seldom infected with any other than *Entameba Histolytica* that we barely mention them. However, this species must be differentiated from the others to prove the diagnosis of amebiasis. The differentiation is based largely on the nuclear structure and morphology in the various stages of the life cycle. In this species we see three distinct stages in its life cycle, which are: Vegetative or trophozoite, pre-cystic stage, and cystic stage. Since each stage differs morphologically, it is necessary to take each one up separately.

VEGETATIVE STAGE: In the vegetative or trophozoite stage of *Entameba Histolytica*, we see motile amebae varying in size from 15 to 80 microns or averaging between 20 to 25 microns (39). These trophozoites are seen only in freshly passed feces that are liquid or semi-liquid in consistency.

The cytoplasm of the amebae is divided into two portions; an outer refractile hyaline portion, the ectoderm, and an inner, less refractile, more granular appearing endoplasm. The ectoplasm is most noticeable when the amebae are moving; it forms the pseudopodia, which appear as glass-like projections from the body of the parasite. The endoplasm comprises more than two-thirds of the body of the amebae, resembling ground glass in appearance and is more coarsely granular than the ectoplasm. This portion contains the nucleus and the ingested bodies; i. e., red blood cells, if there is blood in the stools. The occurrence of red blood cells within this species of amebae is a valuable diagnostic aid. Its diagnostic value was first called to attention by Craig (40), in 1905.

Motility is accomplished by means of pseudopodia formed by finger-like projections of the ectoplasm from the body of the amebae into which the endoplasm rapidly flows and thus movement is accomplished. Motility is quite marked in freshly voided feces, but is lost in stools which are allowed to cool; there also being a change in morphological structure. Thus, it is quite important that we examine a fresh stool when looking for *Entameba Histolytica*, since its motility aids greatly in the diagnosis and in differentiating it from other species of amebae.

PRECYSTIC STAGE: Prior to encystment, the motile or vegetative trophozoite forms of *Entameba Histolytica* lose their motility, become somewhat reduced in size, rid themselves of ingested material such as red blood cells and become spherical or ovoid in shape. In living, unstained conditions, these precystic amebae appear as colorless, hyaline, slightly ovoid bodies measuring from six to twenty microns in diameter. Progressive motility is usually absent, but they may form small blunt pseudopodia, but these are almost instantaneously withdrawn and no movement is observed. The nucleus appears as a visible ring of refractile granules located centrally within the endoplasm. The nucleus is not observed in unstained preparations of the vegetative stage. This form of *Entameba Histolytica* is differentiated with difficulty from the similar forms of *Entameba Coli*. Therefore, the vegetative cultural methods are for their identification.

CYSTIC STAGE: In living, unstained specimens, these appear as colorless, hyaline bodies which are usually round or slightly oval. The cyst has a wall which appears as a double refractile outline. The

size varies from 5 to 20 microns in diameter. The nucleus may be visible as a small refractile mass. The cysts do not contain red blood cells or other ingested material; thus the cytoplasm appearing clear or slightly granular, (41).

Thus we see the life cycle of *Entameba Histolytica* consists of the afore described stages. The portal of entry is by means of the alimentary canal. Cysts of this parasite are swallowed by man, pass through the stomach, not being affected by the gastric acidity in the stomach; then they pass through the entire small intestine, but as it reaches the large intestine the cyst wall is believed to have become permeable and it is here that the cyst wall ruptures. Chatton (42) in 1917, showed that excystation could occur in the small intestine and at this time believed that this was where the process took place, but Sellards and Thieler (43) in 1924, were able to infect kittens by rectal injections of the cysts and produce the typical lesions, thus proving that excystation can occur in the large intestine as well. Their experiment has been repeatedly confirmed by co-workers.

When the cyst ruptures, a four-nucleated amebasis is liberated and gives rise to eight young amebae by direct cell division. Each young ameba becomes motile and is known as a trophozoite (44). The trophozoites attack the mucous membrane of the intestine by a cytolytic substance which they excrete and by means of their ameboid motility. In this manner the mucous membrane of the intestine is dissolved and penetrated by the parasite and the characteristic ulceration of amebic dysentery produced. The trophozoites multiply in the tissues and in the lumen of the intestine, thus increasing the area and extent of ulceration unless

otherwise checked by treatment.

When conditions become unfavorable for the vegetative stage to exist, the trophozoites lose their ameboid motility, round up and discard ingested material, reduce in size and form a stiff wall. These do not invade the tissues but are thrown off the the feces of the host, and which, when again swallowed by man in or on infected food or drink, excyst and become young trophozoites and produce the characteristic lesions in the intestine.

CULTIVATION: *Entameba Histolytica* was not satisfactorily cultured until 1918. However, numerous investigators had claimed to have cultured the amebae prior to this, but Walker (46) in 1911 acknowledged his error and concluded that all amebae sofar cultured from the intestinal tract of man and animals were a free living species and had nothing in common with the parasitic species. Craig (47) in 1912, working independently, reached the same conclusion as Walker, and their conclusions have been confirmed by all observers who cared to study the subject. Thus, we know that many of the cysts of free living amebae are quite resistant to druing and are easily carried about by the wind, thus frequently contaminating food and drink and consequently being ingested by man.

Cutler (48), in 1918, described cultivation of *Entameba Histolytica* on a medium containing blood clot and egg. He obtained cultures from stools of six acute dysentery patients and was successful in sub-culturing the media, if transfers were made very few days, providing that the media did not become acid in reaction. A record of his results

shows sufficient evidence of culturing the amebae and credit for the first successful culturing of *Entamebia Histolytica* has been awarded him by later workers. Boeck and Drbohlav (49) in 1924 successfully cultured *Entameba Histolytica* on Locke solution--egg medium--and were able to maintain the cultures for eight months. They established identity of the cultured organism with those of freshly examined stools. Numerous others have confirmed these results. Since this time Craig (50) and St. John claimed to have had success with a more simple media and state that they have found their methods superior for diagnostic purposes.

MODES OF TRANSMISSION: *Entameba Histolytica* is transmitted from man to man through food and drink polluted with feces containing cysts of the parasite. Only the cysts are infective to man (51). If the motile form or trophozoites, are ingested by man they are readily killed by the gastric acidity. The fact that the cysts are transmitted by food and drink places amebic dysentery in the same category as typhoid fever, bacillary dysentery and cholera.

We are not so much concerned with the individual suffering from acute diarrhea, since the cysts do not usually occur in the stools of such cases. It is in the individual who appears healthy, or the convalescent, who is a source of infection to others, as the cysts form in the intestine under unfavorable conditions and at this time he becomes a carrier. Walker and Sellards (52) in 1917 demonstrated this vital factor in the carrier in the transmission of *Entameba Histolytica*.

Therefore the most common modes of transmission are by contamination of food and drink. This may be brought about by polluted

water supply; through use of human excreta in fertilizing truck gardens, especially in the Orient and many tropical and sub-tropical countries; through droppings of flies as before mentioned; (53), and by infected individuals who are handling the food and excreting the cysts, as shown by Tonney, Hoeff and Spector (54) in a review of the source of the outbreak in Chicago in 1933. Polluted water in swimming pools is also another source by which it may be transmitted.

Thus we can easily see the importance of sanitation and proper disposal of sewage and proper protection from flies and infected individuals, in transmission of the organism. For further reference to the epidemiology I refer you to Craig's Amebic Dysentery and Amebiasis.

PATHOLOGY

In discussing the pathology, we must divide the subject matter into three portions: Pathology of those suffering from amebic dysentery of the intestine; those who are harboring the organism, carriers; and the pathology produced by invasion of *Entameba Hystolytica* into the various tissues and organs of the body.

It is the common belief today that *Entameba Hystolytica* upon admission to the intestine secretes a cytolytic substance which destroys the superficial layer of epithelial cells and gains entrance into the wall of the intestine. This, along with the ameboid movement, enables the organism to invade the wall of the intestine and produce its characteristic lesion. Councilman and Lafleur (55) describe the mechanism of production of the lesions as follows:

"The ulceration appears generally to be caused by the invasion of the mucous membrane by the amebae. They enter this, passing along the interglandular tissue and, in some cases, they enter the glands. The follicles of the glands often show necrosis of the cells with nuclear fragmentation. This is probably due to the action of the soluble products of the ameba."

Dobell and O'Connor (56) in 1921 believed that the organism gained entrance into the intestinal wall by a cytolytin secreted by the amebae. Wenyon (57) in 1926 believed that there was a combined action on the tissues, by mechanical and the cytolytic activity of the amebae.

Craig (58) in 1927 demonstrated that *Entameba Hystolytica* secretes a substance which dissolves the intestinal epithelial cells and red blood cells, by extracting such substances from cultures of the organism. The motility of the organism is well known, so these two factors must play the major role in production of the lesion. Ree's (59) in 1929 was also of the belief that the cytolytic action played the major role. Ratcliff (60) in 1932 believed that the direct mechanical penetration by the amebae and aided by the cytolytic action, was the most plausible explanation in production of the lesion. Thus we see that it is the common belief that the organism does secrete a substance which has a cytolytic action on the intestinal epithelium, and its motility is well known, so the mechanism of production of the lesion is easily understood.

In Councilman's and Lafleur's (61) original monograph published in 1891 they say:

"The ulceration appears generally to be caused by the invasion of the mucous membrane by the amebae. They enter this, passing along the interglandular tissue, and in some cases they enter the submucosa; and in this their action becomes most apparent. The submucous tissue becomes edematous, swells up and softens, and with this softening the ulceration processes begin. The tissue above, deprived of its blood supply, becomes necrotic and falls in upon the cavity of the submucosa. Not only do the ulcers increase by the continual undermining process, but there is probably a continuous softening and liquefaction of the tissue from contents of the intestine."

These studies were so extensive on the subject, and are so complete on lesions of man, that very little has been added to their original description of the lesions.

The lesions are encountered most frequently in the caecum, ascending colon, sigmoid and rectum; according to James (62) in 1928, with his summary of his own cases and with the work from other authentic sources.

Microscopically, the external appearance of the intestine will vary with the extent of the infection. However, it is usually of greyish-white color with areas of marked discoloration scattered along it, ranging from brownish-yellow to almost black. These discolored areas usually mark the site of a lesion, but may and frequently are, due to hemorrhagic extravasations brought about by interference with the circulation, by lesions or secondary infections. In cases where actual gangrene has occurred, the intestine may appear a dusky red in color. Adhesions between the coils are common in the long-standing cases, as well as marked thickening of the intestinal wall. The thickening occurs for the most part in the submucosa, but may involve the other coats as well. If thickening has occurred in isolated areas, the intestine will appear constricted in these areas and may produce a partial obstruction. Usually in such case we see dilatation and sacculations of the gut above the connective tissue hypertrophy.

The primary lesion consists of cytolysis and necrosis of the superficial cells of the mucous membrane in quite small, pin-point or larger areas, accompanied by hyperemia and edema of the surrounding tissues. Perhaps the most characteristic lesion of the early stages appears as nodular areas often at the apices of the follicles of the intestine, showing small pin-point openings on the surface.

The mucous membrane in the immediate vicinity and covering them is congested and may be hemorrhagic. Upon incision of these small nodules they are found to contain a yellowish to greenish, gelatinous, semi-fluid material which microscopically consists of cytolyzed cellular detritus and mucus, frequently showing actively motile trophozoites of *Entameba Histolytica*. The nodular elevations are preliminary to the ulcerations, which develop as the process extends laterally into the mucous and submucous coats of the intestine. The ulcers present a flask-like appearance; i. e., the small openings on the mucous membrane of necrotic tissue and the undermining of the mucous membrane to form the floor on the submucous coat. The ulcer spreads by lateral and downward extension, involving the submucous and even the muscular coats, rather the connective tissue of the musculature, of the intestine (63). The ulcers appear as numerous small punched-out areas with an occasional large undermined area with superficial necrotic mucous membrane. The numerous small punched-out appearing ulcers with the surrounding edematous and even hemorrhagic tissue, present a typical button-hole appearance and are quite characteristic lesions of amebic dysentery (64).

The lesions tend to burrow deeper and deeper until eventually they may perforate through the peritoneal surface of the intestine.

We may see large areas of the intestine involved. The lesions of some standing tend to coalesce by an undermining process and a portion of the "normal" mucosa would be seen between the two lesions.

Healing of the ulcers may occur spontaneously or after treatment. Healing occurs from the periphery inward; the smaller lesions are replaced by mucous membrane, but in the larger ones there is considerable scar tissue laid down to replace the mucous membrane, especially if the ulcers have been numerous. Where we have considerable dense fibrosis, we are apt to have a permanent thickening and rigidity or possible stenosis of the intestine (65).

The scar tissue may also lead to sacculation of the intestine, as has already been stated.

To summarize the types of lesions present in amebic dysentery, we may say that there are three types (66-67); the nodular thickenings situated at the summits of the folds of the mucous membrane, which when incised are found to be filled with a viscid, gelatinous material which usually contains motile trophozoites of *Entameba Histolytica*; ulcers having thickened walls and presenting shaggy, yellowish brown edges which are always undermined. These are covered with a necrotic mucous membrane which on removal reveals the interior of the ulcer filled with a brownish yellow material or pus; the almost invariable presence of coalescence of the lesions with sinuses connecting the various ulcers under apparently normal mucous membrane.

Craig (68) believes that these three types of lesions are diagnostic of amebic dysentery and all types may be present in an individual case.

A microscopic section of the lesions will show massed infiltrations with endothelial cells, lymphocytes, and rarely, leucocytes. Numerous motile or encysted forms of *Entameba Histolytica*

may be found throughout the section. We see a marked degenerative, cytolic change in the cells, which are usually surrounded by a serous exudate which not infrequently contains red blood cells. It cannot be too highly stressed that the presence of leucocytes is rarely observed in uncomplicated cases of amebic dysentery (69).

AMEBIC LESIONS OF THE LIVER: The most frequent site, with the exception of the intestine, of invasion is the liver. The amebae are undoubtedly transported to the liver through the portal system (70). However, post-mortem examinations may show numerous trophozoites in the adjacent lymphatic vessels of the intestine, but it is highly improbable for them to reach the liver through this route. The abscesses are usually multiple and are most frequently seen in the right lobe of the liver; this being undoubtedly due to the anatomical relationships.

Microscopically, the liver may appear normal in size, but is most generally enlarged and shows marked venous congestion. If the abscesses are in contact with the peritoneum, there may be a local peritonitis and adhesions may have formed between the adjacent organs. On cut section the liver may present areas of grayish-brown color, soft in consistency and having a worn or moth-eaten appearance. These represent the necrotic areas produced by the cytolytic action of *Entameba Histolytica*. Material obtained from such areas will show motile trophozoites of *Entameba Histolytica* and on section will show marked cytolysis of tissue, an accumulation of fibrin, lymphocytes, connective tissue cells and red blood cells, and lying in the connective

tissue framework trophozoites will be irregularly scattered throughout the material.

Surrounding these areas we see an area of hyperemia, but no definite abscess wall. As cytolysis and necrosis proceed, the abscesses contain a very characteristic material. It consists of a semi-fluid, yellowish-red or chocolate colored mass consisting of shreds of necrotic liver tissue, red blood cells and cytolized connective tissue cells.

This is the typical picture of amebic abscess without secondary infection. If secondary infection should occur, we may see all the aforementioned and a yellow or greenish-yellow purulent material. We must remember that pus is not seen in pure amebic abscesses; the exudate consisting of cytolized liver tissue mixed with shreds of tissue and red blood cells.

Early, we see only an area of hyperemia surrounding the lesion, but later as the process continues, a definite connective tissue wall may be observed about the abscess.

Microscopically, the picture is one of progressive necrosis of the parenchymatous cells of the liver, followed by dissolution of the connective tissue framework. The process extends radially as the amebae advance, leaving a zone of collapsed stroma between the normal liver tissue and the necrotic area (71). Thrombosis of the blood vessels at the periphery occurs and may be a factor in extension of the abscess, particularly toward the periphery of the liver. Trophozoites may be seen in the abscess wall in the zone of necrosis, usually near the connective tissue border (72). Here again

we see none or relatively few leucocytes, since as previously mentioned, amebiasis is a cytolytic reaction rather than an inflammatory one. However, secondary infection with pyogenic organisms has and may occur, which will almost entirely displace the picture of amebic abscess and show that of an inflammatory one. This is estimated to occur in about 40% of the cases, by eminent authorities. The usual bacteria associated with amebic abscesses are the staphylococcus, streptococcus and bacillus coli.

AMEBIASIS OF THE LUNG: The liver is not the only organ that may be affected by the parasite. The lung is the third most common site of localization of amebic lesions. They may, and usually do, reach the organ through the blood stream, possibly embolic in origin as was first demonstrated by Bunting (73) and later confirmed by Strong (74). He traced emboli containing ameba from thrombosis of the hepatic vein to emboli of the pulmonary arteries. Rupturing of liver abscesses through the diaphragm and into the lung is encountered frequently. Obviously the right lung would be the most common site of abscess formation. First a local pneumonia occurs, with rapid abscess formation. The abscesses of the lung are usually single unless several emboli have lodged in various portions at the same time. Microscopically, we see the mucoid and gelatinous material that is typical of amebic lesions, together with the red blood cells, amebae, large mononuclear cells from the walls of the alveoli and fragments of elastic tissue of the lung. The lesions may rupture into a bronchus and the contents be expectorated in a brownish, mucoid material containing blood corpuscles and the trophozoites.

Amebic lesions of the lung are seldom recognized before considerable lung tissue is involved, and most generally only at autopsy.

AMEBIC LESIONS OF THE SKIN: According to Engeman and Mileney (75) the fourth most common site of amebiasis is the skin. Such lesions may occur after surgical drainage of an amebic abscess, drainage of ruptured appendix or perforated colon, direct extension of rectal ulcers or through the anus by a fistulous tract. He believes that they probably would never occur if the primary condition was early recognized and treatment instituted.

Amebic infection of the skin is manifested by a rapidly spreading, intensely painful ulceration. The lesion spreads most rapidly in the subcutaneous tissues, leaving overhanging areas of necrotic skin with a surrounding area of hyperemia.

Macroscopically, the pathological picture is atypical due to secondary bacterial invasion. The scrapings of the ulcers will show forms of the amebae, though, and this is our only way of diagnosing the condition. They find the pathology quite similar to that found in ulcerations of the intestine. In cases where secondary bacterial invasion has not occurred, the process is one of cytolysis and direct extension with absence of the usual signs of inflammation other than the hyperemia surrounding the ulcer. A few leucocytes may be seen, but are in no way a criterion to the severity of the lesion. Motile forms of *Entameba Histolytica* are readily observed in scrapings of the lesions. However, we seldom see a

cutaneous ulcer of any sort that does not become secondarily infected, and when this occurs the pathological picture is somewhat altered. Here we see a mixture of inflammatory and cytolytic destruction, so it is therefore necessary to find the amebae before a diagnosis can be made.

Recent investigators have found that practically every organ and tissue of the body may be invaded with *Entameba Histolytica*. However, there is some question as to the authenticity of their reports; but knowing that the organisms do enter the blood stream, we can readily see where it would be highly possible for the organism to invade any tissue of the body. Kofoid and Swezy (76) have performed considerable experimental investigations on this subject. Although their reports have not been confirmed by recent investigators, it is in my opinion possible for *Entameba Histolytica* to invade any tissue or group of tissues in the human body.

The urine in amebiasis is usually clear, but in long standing cases may show some albumin and hyalin casts. Nephritis is a not uncommon complication of the disease, so urinary findings may be quite typical of a nephritis.

The blood picture (77-78) may show a mild anemia; 4,000,000 to 4,500,000 red cells with a reduction of the hemoglobin from ten to twenty points. In some cases the red blood count is normal owing to the concentration of the blood following post-diarrhea déhydration. The white blood count usually shows some elevation, ranging from 10,000 to 20,000 cells per cubic millimeter. In the

cases with a high leucocyte count, one should always suspect a liver abscess. The differential susually shows a slight increase in polynuclear cells. Eosinophilia is rarely observed. If an eosinophilia is present it is highly probable that some organism other than Entameba Histolytica is the exciting factor.

SYMPTOMATOLOGY

The clinical course pursued by Entamebic dysentery is in general one of wide variability. In regions where the disease prevails endemically, all grades of severity are constantly to be observed, ranging from the mildest degrees of bowel derangement to the most evident attacks of acute fulminating dysentery. On the other hand, fairly extensive ulcerative lesions may be present in the intestine without producing definite symptoms. Nevertheless, even in such cases careful questioning will usually reveal a history of some slight derangement from the normal bowel functioning; generally intermittent in character.

The irregularity and inconstancy of clinical manifestations exhibited by the disease are determined by a number of factors; the location and extent of the lesion, the reaction of the individual to infection with the organism, the varying changes in morphology exhibited by the organism during the evolution of its life cycle within the human body. Of these factors, the changes in morphology exhibited by the organism exert by far the most marked effect upon the clinical course of the disease. During the vegetative stage of the organism, rapid extension of the lesions occurs, producing active clinical symptoms, and it is at this period that the patient experiences recurrences in varying degrees of severity.

When the environment is rendered unsuitable for the vegetative state of the organism to exist, the smaller and less active and more resistant precystic state of the organism is developed as a result. It is this form of the organism that is ordinarily found in the stools during convalescence from the more acute attacks. The organism undergoes still another change in morphology; the cystic stage. The cystic forms are found to occur during the quiescent stage of the disease, when the clinical manifestations remain for the most part in abeyance. The cysts are passed in the stools and it is by this means that further perpetuation of the species within a new host is possible.

The clinical aspects of the disease may be conveniently grouped for consideration under the following headings: The so-called carrier state, acute amebic dysentery and chronic amebic dysentery.

There is no such thing as a healthy carrier. These individuals are harboring the organisms and will show some degree of pathology of that previously described. According to Craig's (79) experience, the symptomatology of amebiasis in the so-called carrier is confined to the gastro-intestinal tract, circulatory and nervous systems. Other authorities have at some time described symptoms referable to the eye and other organs of special sense.

The symptoms referable to the gastro-intestinal tract are evanescent attacks of diarrhea with mild colicky pains in the lower abdomen or the right iliac region, anorexia or a capricious appetite, gaseous distension of the abdomen after eating, gaseous eructations, constipation, and slight nausea before eating or directly afterward.

The symptoms most often noted in the nervous system are neuralgic pains in the lower abdomen, back or legs; dull frontal headache; sleepiness or disturbed slumber; poor memory and lack of ambition; dull, aching muscles, usually in the legs and especially in the mornings upon awakening. The symptoms noted in the circulatory system are an irritable pulse; arrhythmias; vaso-motor disturbances such as flushing of the skin and excessive perspiration of the hands and feet; and tachycardia.

The physical signs most often noted in carriers are: Underweight, sallow skin, slight anemia, irritable pulse, tenderness on deep pressure over localized areas of the large intestine, tenderness in the right iliac fossa, distension of the abdomen, and in some cases, tenderness over the liver.

^{analysis}
ANALYSIS OF SYMPTOMS: Abdominal distention due to gas is one of the most common symptoms noted in carriers and probably occurs in every case. The distention is most marked after eating, and gradually increases for several hours and is accompanied by gaseous eructations and the passing of large amounts of flatus through the rectum. The distention may be painless or be accompanied by slight colicky pains or attacks of discomfort. The distention does not come after every meal, but is noticed most often after partaking of a large meal or certain articles of food which in the normal individual never cause distention.

Constipation is a frequent symptom of the disease and is found to be the rule rather than the exception. It may be almost

constant or occur at intervals; sometimes alternating with evanescent attacks of diarrhea.

Diarrhea frequently occurs in carriers, but is seen less frequently than is constipation. Frequently a patient may be constipated for weeks or months and have an attack of colicky pain in the lower abdomen, usually at night, followed by loose stools for two to three days, with relief of pain. Some of the so-called carriers never show constipation or diarrhea but have a daily bowel movement of semi-solid stools.

The appetite is usually a capricious one; the patient being very hungry at times, and again without any desire for food and when he does eat the food doesn't seem to taste good; or a small amount of food may produce a feeling of nausea or sensations of fullness and distension, with gaseous eructations. This type is so often diagnosed as chronic indigestion or dyspepsia.

Loss of weight is quite often observed in carriers, especially if the organisms are present in sufficient quantities to produce symptoms. Patients usually lose weight during the summer and regain their weight again in the winter months.

Headache is not at all uncommon and occurs as a dull, boring type, almost invariably frontal in location. It is usually present almost constantly for days or weeks, or it may occur at intervals and last only for a day or two.

Sleepiness or disturbed slumber is frequently noted in carriers, but insomnia rarely occurs. Many individuals harboring the parasite experience difficulty in keeping awake during

the day, especially if their occupation is of sedentary nature. Through the night they do not rest soundly, often disturbed by dreams and awakening frequently, and rising in the morning unrefreshed by the night's sleep.

Sallow skin, according to most observers, is quite marked in carriers of *Entameba Histolytica*. James and Deek (80) 1925, have called attention to the doughy, inelastic skin of several individuals showing symptoms of amebiasis unaccompanied by dysentery. This symptom is also marked in other chronic ulcerative or inflammatory conditions of the intestine. It is, however, considered of value in diagnosis of amebiasis.

Localized abdominal tenderness is another common finding in carriers. The tenderness is not always extreme, but usually described as a soreness over the appendix region, ascending and descending colon.

Symptoms of poor memory and lack of initiative are not at all uncommon, but we would expect this in this, as well as in other long drawn out diseases.

Fever in carriers is, according to most observers, subnormal in the morning and slightly elevated in the afternoon; resembling that of chronic tuberculosis.

These symptoms are not pathognomic of carriers, but it is this type of history from the patient that should lead one to examine the stools and make a subsequent diagnosis of amebiasis. The value of gastro-intestinal disturbances cannot be too highly emphasized, and in every case the stools should be repeatedly examined

for amebae, where no definite pathological lesion has been found.

The incubation period varies considerably in a vast majority of cases. Infection of the intestinal tract with the *Entameba Histolytica* covers a protracted period. The initial onset of the disease does not, in fact, bear any direct relationship to the inception of the infection. This fact has been demonstrated by Walker and Sellards (81) 1913, with their feeding experiments of human volunteers. They concluded that the incubation period may vary from a few days to 95 days and if they were not infected by this time they were immune. O'Connor's (82) work in the Chicago epidemic of 1933 shows that the incubation period was only a few days to 18 days. However, he concluded in his paper that this was due to the enormous dosage of cysts ingested by the individuals and that this is seldom the case.

SYMPTOMS OF ACUTE AMEBIC DYSENTERY: In this type the onset is spontaneous and the course of the disease is frequently of a highly acute, fulminating character. The patient is attacked suddenly, often in the midst of good health, but may have had history of previous attacks. The patient is usually seized with sudden acute abdominal pain followed by a severe diarrhea; the stools containing much blood and mucous from the beginning. In some cases there is considerable fever resembling the onset of acute bacillary dysentery; more frequently, however, the dysenteric symptoms begin after an attack of diarrhea lasting a day or two. The patient may notice blood and mucous in his stools over a long continued attack of diarrhea and may recover spontaneously without further dysenteric symptoms, or the attack may

progress into a well developed case of amebic dysentery. In most cases of amebic dysentery occurring in temperate zones, with the exception of occasional epidemics, the onset is gradual; but in the tropics the onset is more sudden and the prostration is much more severe.

FEVER: In temperate climates fever is usually present at the onset, but the disease becomes more chronic the fever becomes slightly sub-normal, with slight afternoon elevations, as in the case of carriers. Fitcher (83) 1903, in an analysis of twenty cases observed a fever of 100-102 degrees F. at the onset with a gradual drop to slightly below normal as the case became more chronic, in uncomplicated cases. It has been the belief that fever did not occur in uncomplicated cases; however, this is obviously quite unusual and most observers agree today that there is an elevation of the temperature where the ulcers are secondarily invaded by pathogenic micro-organisms. It is my belief from a review of the literature that there is a slight elevation in temperature in uncomplicated cases, although not high, and there may be considerable rise in complicated cases, depending on the degree of ulceration and toxic absorption. Chills are seen in the acute fulminating types, but seldom seen in usual cases. The chills are not, as a rule, severe, and seldom last over one-half hour.

ABDOMINAL PAIN: In many cases acute abdominal pain ushers in an attack of acute amebic dysentery. The pain is usually colicky or cramp-like in nature and occurs in the lower half of the abdomen. The pains may be more severe just preceding the bowel movement and tend to let-up between movements. Abdominal tenderness, either general or localized, is a frequent symptom. Tenderness is usually most marked

over the caecum and the ascending colon and over the sigmoid portion of the colon.

Nausea and vomiting may occur in cases with a sudden onset, and may closely resemble an obstruction at first, but this may be easily differentiated.

The appetite is usually lost and anorexia may be present.

The number of bowel movements may vary from six to eight in 24 hours in the milder cases and in the acute cases as high as 30 to 40. The average case usually has in the neighborhood of 15 bowel movements per day. The bowel movements are, as will later be described, scanty in amount and semi-fluid in consistency.

Tenesmus: Fitcher (84) believes that tenesmus may occur, but it is rather the exception than the rule. This is because the rectum is usually not involved, the lesions being most marked in the caecum and ascending colon. However, this might be the main reason for the patient coming to the doctor, and certainly should deserve consideration.

Emaciation is usually quite rapid in the acute cases with numerous stools lasting several days. The patient's skin is marked sallow, anemic appearing and according to some observers, there may be slight jaundice and tenderness over the liver area. This should suggest the beginning of abscess formation in the liver, especially if accompanied with fever and leucocytosis.

SYMPTOMS OF CHRONIC AMEBIC DYSENTERY: Chronic amebic dysentery presents similar symptoms to the acute form, varying somewhat in the

severity of the disease. However, chronic amebic dysentery is characterized by remissions or relapses with periods of constipation alternating with diarrhea. If the patient has a number of relapses, the diarrhea has a tendency to persist and the patient's stools never become well-formed.

The skin presents a characteristic greenish or sallow hue, and anemic appearance. It is this type of case in which secondary infection is apt to occur and the symptoms of an enteritis may mask those of amebic dysentery. The symptoms are very much like those described in carriers.

Death is usually due to exhaustion or a complication of the disease. Of course there is the possibility of an intercurrent infection, which is undoubtedly very great, because of the lowered resistance of such cases. The most common cause of death in such cases is broncho or lobar pneumonia.

DIAGNOSIS OF AMEBIC DYSENTERY

Clinically it is almost impossible to make a diagnosis of amebic dysentery because the symptoms are so easily confused with numerous other manifestations of the intestinal tract, such as bacillary dysentery, ulcerative colitis of varied etiology, carcinoma of the rectum or lower bowel, tuberculous enteritis or colitis, Balantidiasis and other forms of flagellate infections of the bowel, and other systemic diseases as sprue and pellagra and numerous others which cause a disturbance of the intestinal tract. Thus an ultimate diagnosis must depend upon the demonstration of the vegetative or cystic forms of *Entameba Histolytica* in the stools of the individual. It is by this means only that we can confirm the diagnosis, and should resort to this without fail indoubtful intestinal conditions.

Technic for stool examination: The whole stool should be examined if possible. Microscopically, the stool of amebic dysentery is quite characteristic. It may be described as a reddish-brown or chocolate stool, containing blood and mucous. The blood is usually dark, giving the appearance of vomited blood or coffee-ground appearance, with the exception of an unusual case where there may be considerable bright red blood due to sudden erosion of an artery. The stools of acute exacerbatations are usually fluid or semi-fluid in consistency and with the naked eye one can see shreds of mucous mixed with the fecal material. However, not every case under observation will give

the so-called typical bloody-flux stool; sometimes the stool being formed with evidence of but little blood, but even in these cases we often see blebs of mucous intermingled with the fecal material, which is ~~the~~ characteristic. The stools should be examined while still warm, because the vegetative forms lose their motility and undergo degeneration within a short time after being exposed to the air and cooled.

If the patient is passing formed stools, most authors believe it best to give them a saline cathartic such as magnesium sulphate, the evening before and obtain the first stool on the following morning. One should never attempt to examine a stool specimen for *Entameba Histolytica* after the patient has taken oils of any kind, due to distracting factors which may occur in the stool; nor should one attempt to examine the stool after urine has been passed into the container.

After having made the gross observations of the fresh stool, microscopic examinations should be made. For general considerations it is unnecessary to stain the specimen. The stool should be thoroughly mixed and a capillary loop may be used to transfer the specimen to a clean dry slide on which a drop of normal saline has been previously placed; these should be mixed and then examined. Most authors prefer to place a cover glass over the medium and have the solution transparent enough so that newspaper print can be read through it. One should examine at least two to four ~~cover~~-glass preparations before a negative report is made. The organism itself is quite transparent, which necessitates cutting down the amount of light under the scope. If the stool is formed, specimens should be taken from several

portions and dissolved in normal saline solution prior to examination. One may use a concentration method if no amebae have so far been found. It is the opinion of several authorities that the stool should never be pronounced negative until the concentration method has been used. This procedure can easily be performed by dissolving larger portions of the stool in saline, filtering through gauze filter, centrifuging and then proceeding with the routine microscopical examination.

If ameboid organisms are observed under the microscope, we are confronted with a differential diagnosis of the various amebae which most commonly occur in the intestine of man. In routine diagnostic work there are three species that in most cases have to be differentiated. They are *Entameba Histolytica*, *Entameba Coli* and *Endolimax Nana*, while *Iodameba Butschlii* and *Dientameba Fragilis* may be practically ignored, because of their rare occurrence (85).

Entameba Histolytica can be differentiated from *Entameba Coli* and *Endolimax Nana* in both vegetative and cystic stages of development. The morphology of fresh, unstained and stained preparations may be relied upon for differential diagnosis.

The following table will be found useful in differentiating the essential differential points.

VEGETATIVE UNSTAINED SPECIMEN

<i>Entameba Histolytica</i>	<i>Entameba Coli</i>	<i>Endolimax Nana</i>
Size-----18-60 microns Average 20-35	15-50 microns Average 20-30	6-12 microns Av. 8 microns
Motility----Active, progressive and directional	Sluggish, rarely progressive and seldom directional	Sluggishly Progressive
Pseudopodia-Finger-shaped, clear and glass- like	Shorter, more blunt, less glass-like in appearance.	Broad, blunt, not glass-like

E. H.	E. C.	E. N.
Inclusions---red blood cells when feces contain blood. No bacteria in fresh specimens.	Numerous bacteria, crystals and other materials. No red blood cells.	Numerous bacteria. No red blood cells.
Nucleus-----Invisible	Visible	Visible

VEGETATIVE STAINED SPECIMEN

Nuclear Membrane	Delicate; inner surface has single layer of minute chromatin dots.	Thicker; inner surface lined with coarse chromatin dots.	Not so thick; chromatin dots rarely seen.
Karyosome	Very small. Usually in center of nucleus	Large, situated eccentrically	Large and may be divided into one large and one small mass; situated at side or center of nucleus.
Intranuclear chromatin	No chromatin between karyosome and membrane.	Chromatin between karyosome and nuclear membrane	No chromatin between karyosome and membrane.
Inclusions	Red blood cells, no bacteria in fresh specimens.	No red blood cells, many bacteria and other material.	No red blood cells, many Bacteria.

CYSTIC STAGE

Size	6-20 microns average 7-15	10-20 microns average 12-18	5-10 microns
Shape	Gen'l. spherical, may be oval and rarely irregular	spherical, rarely oval or irregular	spherical, oval or illiposoidal
Nucleus	One to four, minute with karyosome in center.	One to eight, eccentric karyosome.	One to four large, Karyosome central.

*(85) Note taken from Craig's Amebiasis and Amebic dysentery.

Thus if an ameba is found in the feces of man, which is actively motile, the motion being progressive in character, having well-formed finger-shaped pseudopodia and containing red blood cells in its cytoplasm, the diagnosis of *Entameba Histolytica* is justified. Even though the red blood cells are not observed in the cytoplasm, most authors believe the motility and the characteristic pseudopodia sufficient to justify a diagnosis of *Entameba Histolytica*.

DIFFERENTIAL DIAGNOSIS: Bacillary dysentery is undoubtedly the most common and important disease that might be confused with amebic dysentery. The onset of bacillary dysentery is usually sudden, with previous health having been good, while the onset of amebic dysentery, even though sudden, is usually preceded by a period of intestinal disturbance and diarrhea. However, as shown with the Chicago epidemic of 1933, several cases had a very sudden onset with no history of previous intestinal disturbance. It is believed that these people received much larger doses of the cysts from the heavily polluted drinking water than is ordinarily the case. It may therefore be said that a dysentery of sudden onset without previous symptoms, especially if accompanied with much fever and evidence of toxemia, is very suggestive of bacillary dysentery. Then too, we must bear in mind that from 5 to 10 percent (86) of the individuals in the United States harbor *Entameba Histolytica*, so we may observe amebae in stools of patients suffering from acute attacks of bacillary dysentery, or the two diseases occurring together.

In most cases of bacillary dysentery the symptoms are more acute, the patient appears more toxic, and the number of stools is greater and tenesmus is more marked than in amebic dysentery.

The course of bacillary dysentery is usually shorter, lasting only a few days; while with amebic dysentery the course is usually chronic, with relapses and acute exacerbations.

The stools of each type are quite characteristic; those of bacillary dysentery are fluid, often containing little fecal material, consisting for the most part of mucous and considerable blood which is often partially laked; while with amebic dysentery the stools usually contain much fecal material mixed with mucous and blood.

Microscopically (87) the stools of amebic dysentery contain comparatively few pus cells and the leukocytes present marked evidence of cytolysis. The red blood cells, when present, occur in clumps and Charcot-Lyden crystals may be present. While with bacillary dysentery, the exudate contains multitudes of pus cells, 90% of the cells present being degenerated leukocytes, the nuclei of which show marked toxic degeneration, while large mononuclear macrophages may be present which may contain red blood cells. These are constantly being mistaken for amebae, but are easily differentiated by their lack of motility. One should never warrant a diagnosis of amebae unless under the stained specimen he can demonstrate the morphology of the amebae, especially so in cases where there is no motility.

Balantidal dysentery, the rare form of dysentery due to the invasion of the intestine by *Balantidium coli*, a ciliate belonging to the protozoa, is indistinguishable clinically from amebic dysentery, and differential diagnosis must be made by demonstration of the causative organism in the stools. The disease being relatively rare and amebic dysentery quite common and the morphology of the two organisms is so

characteristic that a differential diagnosis can easily be made under the microscope.

Chronic ulcerative colitis presents a clinical picture which very closely resembles that of amebic dysentery and it is considered impossible to make a differential diagnosis without the aid of the laboratory. A proctoscopic examination may be of some aid in diagnosis, but repeated stool examinations would be necessary to disprove the possibility of amebic dysentery.

Other diseases such as tuberculosis, malarial dysentery, malignancy and so on, depend on well known methods for their recognition and diagnosis. All cases presenting a clinical picture similar to that of amebic dysentery always deserve repeated stool examinations and even though we find the organism, we cannot be too certain that the symptoms are due to the parasite. However, in this case the patient certainly deserves routine treatment to rid himself of the parasite.

Serological tests have been described (88-91). This is a method very similar to that of the complement fixation test for syphilis. An alcoholic extract of the cultures of *Entameba Histolytica* is used. It is necessary to use great care in filtrating this antigenic extract for hemolytic qualities, anticomplimentary qualities and antigenic strength. The technic of the test is important and should not be attempted by inexperienced serologists. The practical value of the test is therefore limited, particularly by the difficulty in preparation and in filtrating the antigenic extract. The test is of little value to the general practitioner because of this and since it does not give a positive reaction in every case.

PROGNOSIS: Of the early cases, approximately one-third are cured with a complete course of emitine; the remaining two-thirds necessitating another course, and then cure is doubtful. However, the symptoms usually subside but the patient is subject to relapses. If the disease has not become chronic in nature it is doubtful whether or not the intestine ever will return to normal conditions. Thus one can easily state that the mortality is relatively low, but the morbidity is relatively high.

COMPLICATIONS AND SEQUELAE OF AMEBIC DYSENTERY

Amebic abscess of the liver is the most common complication of amebic dysentery or amebiasis, the organisms reaching the liver through the portal system, although they may reach the organ by direct extension through the peritoneum. Some authorities believe that they may also reach the organ through the lymphatics, but the general concensus of opinion is that this is a very rare route of infection, if it occurs at all.

The incidence of this complication is said to be from 23% to 59% of cases; however, this estimation was taken from autopsy findings. This being a variable percentage found by the following men: Kartulis (92) in 1887 found it to be present in 55% of 500 cases; Strong and Musgrave (93) found the complication in 23% of 1900 cases; Zancaral (94) in 1893 in 59% of 400 cases; Sitsen (95) in 1927 found 22 cases to have this complication out of 221 cases; Craig (96) observed the complication in 33% of the cases. We must remember that this is an observation of all autopsy cases, and not that of all individuals affected; therefore if we were to take all cases, the incidence would be a great deal lower. Most authorities agree that it occurs in from 1 to 6 percent of all cases of amebic dysentery, varying with the time that treatment was instigated. At present, since more is known about the disease, the actual percentage of liver complications is not over 3% of all individuals harboring the organism.

The symptoms of amebic abscess of the liver differ considerably in different individuals. The onset of symptoms may be sudden, but more commonly is gradual during an attack of amebic dysentery, or in carriers of the parasite. Rogers (97) has laid particular stress on the fact that amebic abscess of the liver has and can occur without any preceding symptoms of dysentery, but we know that they must harbor the organism and that they must pass first through the alimentary canal.

The first symptom# usually noted is pain at the onset of a dull aching character, gradually becoming piercing and stabbing-like in nature as the condition progresses. The location of the pain varies; it may be directly over the liver or in the epigastrium or lower axillary or scapular regions. While in several instances the pain is not noted by the patient until there are several large abscesses in the liver.

The second most common symptom developing usually after the onset of the pain, is fever. As has been previously stated, fever in uncomplicated amebic dysentery is rare; if present at all it is usually very slight. However in acute cases where dehydration is severe, we are apt to have some fever, but of a low grade. The usual case of liver abscess shows a fever which is remittent in type, ranging from 100 to 102 or higher. If secondary bacterial invasion has occurred, the temperature is apt to be high and of a more septic nature.

The third important symptom is the presence of leukocytosis. It should be remembered that a marked leukocytosis is seen in amebic hepatitis before abscess formation has occurred. The

observations of Fitcher (98) in 1903, Biggan and Ghalioungui (99) in 1933, Elliot (100) in 1915 and Craig (101) in recent years, all working individually; find that the count may vary from 15,000 to 20,000; the average being about 18,000 cells per cubic millimeter. They also observed that in cases with secondary bacterial invasion that the white blood count may go as high as 80,000 or higher, or if it develops into a fulminating septicemia we may have a marked leucopenia. We usually see a slight increase in the number of polymorphonuclear cells. Eosinophilia has been observed by some authors, but believed not to be of value other than in differential diagnosis.

Chills, nausea and vomiting are frequently observed with profuse sweating and remission of fever, which often leads one to think of malaria.

The pulse rate is usually elevated to 90 or 130 and dyspnea may be quite marked, especially so if involvement of the lung or pleura has occurred.

The physical signs of amebic abscess of the liver will vary with the size and location of the lesion. We usually see more or less tenderness and rigidity over the liver area; the liver is usually enlarged and if the abscess is superficial one may observe nodulation of the liver. Respiratory movements are usually limited on the affected side. We also see marked cachexia in long standing cases.

Diagnosis: The clinical symptoms of the disease are subject to so many variations, and in fact, the entire course may be so insidious that the first indication of the serious nature of the malady is revealed by the sudden perforation of the abscess into some neighboring

organ. It is a golden rule in the tropics to think of hepatic abscess in all cases of progressive deterioration of health, and to suspect liver abscess in all obscure abdominal cases associated with evening rise of temperature, and this particularly if there be enlargement or pain in the liver, leucocytosis and a history of dysentery. If doubt exists, there should be no hesitation in having early recourse to the aspirator to clear up the diagnosis.

Almost every type of enlarged liver has been mistaken at times for Entamebic abscess. The confusion exists more so in inflammatory swellings where a high leucocyte count is present. The relatively low polynuclear count in amebic abscess may offer some aid. In all cases in which the diagnosis is uncertain, the exploratory needle or aspirator should be resorted to.

The X-Ray has been employed in recent years as an aid in the diagnosis of liver abscess. Under the fluoroscope the diaphragm will often appear fixed and immovable over the dome of the liver. The liver shadow may show marked enlargement.

We may conclude that in cases of liver enlargement following a history of dysentery, we must ~~think~~ think of amebic abscess and with the increased blood count, fever, chills, one should have little difficulty in making the diagnosis. However, if in doubt, as previously stated, one should resort to aspiration to confirm his conclusions.

THE LUNG: The lung is the next most common site of abscess formation. It may occur as a result of *Entameba Histolytica* entering the blood stream, or through direct extension of an amebic abscess of the liver

passing through the diaphragm and pleura.

The symptoms of amebic abscess of the lung are similar to those of pulmonary tuberculosis. The invasion of the lung is accompanied by daily intermittent fever, with slight chills and sweats, especially at night. Usually a cough, as the abscess develops, with an increasing amount of sputum which may contain blood and motile forms of *Entameba Histolytica*. The physical signs are the same as those found in pulmonary tuberculosis, as which the condition is often diagnosed; in other words, the condition is seldom recognized before death.

Amebic abscess of the brain has occurred, but has been reported by only a few observers. Forty-eight cases in all have appeared in the literature. This complication most frequently is a sequela to liver abscess, probably reaching the brain by the vascular system. The lesion may involve any portion of the brain. The symptoms will vary with the location, as will the physical findings. This condition is seldom recognized until autopsy.

Amebic ulceration of the skin can occur and has been thoroughly confirmed by numerous observers (102). Ulcers of this type usually occur following drainage of an amebic abscess of the liver (103), following drainage of intestinal lesion (104), or lateral spreading of an ulcer where the anus and rectum are involved (105), while on the other hand some occur without any direct connection.

Clinically the characteristics of amebic invasion of the skin resulting in ulceration and necrosis, varies considerably and they present a close similarity to ulcerations occurring from other causes. The lesion appears as a rapidly spreading ulcerative process, showing varying activity in different portions of the margins, with an

irregular border which is marked undermined. The overhanging edge of necrotic epidermis from under which purulent material may be expressed, and motile forms of *Entameba Histolytica* observed. The advancing halo beyond the margin of the ulcer is at first a dusky red inccolor, which gradually blends into the normal skin. There is considerable pain and tenderness on pressure over the invaded areas and the tissue is markedly edematous. The floor of the ulcer is composed of granulation tissue, debris and purulent material (106).

APPENDIX: Amebic appendicitis is a not infrequent complication of amebic dysentery. Since the amebae involve the caecum, they may also invade the appendix region and produce symptoms of appendicitis in nearly every way.

Strong (107) in a series of 100 fatal cases found that the appendix was involved in seven cases. Clark (108) found 76 ulcerative appendices at autopsy on 186 cases. Craig (109) also in a study of 60 cases noted that no less than 16 presented symptoms of appendicitis. From these observations it may be concluded that appendicitis is not an infrequent complication of amebic dysentery.

The diagnosis is made with difficulty, because the symptomatology so closely simulates a typical case of appendicitis even though the process is not inflammatory in nature. However, with a previous history of diarrhea and constipation, one should consider the possibility in a differential diagnosis, since surgical measures in such cases are usually disastrous but the condition responds quite readily to routine treatment.

PERFORATION OF THE INTESTINE: Has been known to occur and is occasionally the cause of death in long continued cases. However, when considering the number of individuals harboring the organism, it is rarely that we see this complication.

Intestinal hemorrhage is thought to be relatively rare; even though we do see massive ulceration in the bowel, Strong (110) in his studies noticed only two cases of death from intestinal hemorrhages. It is highly possible and probably true that hemorrhage does occur, but seldom is a large artery eroded and sufficient blood lost to be the immediate cause of death.

There are numerous other complications of amebic dysentery that may occur. In fact nearly every system in the human body has at one time or the other been observed to have been involved.

GENERAL PROPHYLAXIS AND TREATMENT

Amebid dysentery, like other infectious conditions of the intestinal tract, nearly always arises from the swallowing of contaminated food or drink. The chief infectious agent is now recognized to be the encysted form rather than the vegetative form, since the latter is readily destroyed by the action of the gastric juice and in addition, cannot withstand the destructive influences outside of the body.

When conditions become unfavorable for the vegetative forms of the organism, encystment occurs and the cysts are eliminated in the feces. The cystic forms are highly resistant to external conditions and remain viable for an indefinite period after they are discharged from the body, if afforded protection against sunlight and dryness. From the soil, the cysts are distributed by various means to supplies of drinking water and foodstuffs.

Flies and other insects serve as the chief disseminators of the infection. As it has been stated, flies if allowed to feed on the infected feces are able to ingest the cystic forms into their intestines and pass them unaltered in their droppings on any kind of food on which they may feed. It is for this reason quite obvious that the importance of directing stringent sanitary measures toward destroying the breeding places of flies and limiting the uncontrolled distribution of these and other insects in the homes and eating-places of human beings, cannot be too highly emphasized.

In general, the measures employed in the prophylaxis may be summarized under the following headings: The destruction of the organisms within the human body by early instigation of treatment and close observation of the convalescent and so-called carriers of the organism; the destruction of the organisms, especially the encysted forms, following their evacuation from the body and directing measures toward the prevention of contamination of the soil with the cysts; the safeguarding of all potential sources of infection from contact with flies and other insects, and advising the infected individual to follow these measures and to return for repeated stool examinations.

TREATMENT: The contributions that have been made to our knowledge in recent years have been numerous. As a result of these additions to our knowledge of the treatment of amebiasis and amebic dysentery, the literature described in most of our textbooks on the general subject is obsolete because they have treated the symptom complex and those suffering from the more acute forms of the disease and little has been mentioned about carriers or those harboring the organisms with or without symptoms. It is these individuals who are quite obviously the most important factors in spread and control of the disease.

The proper form of treatment of patients suffering from the effects of the organism still remains a question of considerable debate and discussion. Drugs which will give immediate relief from acute symptoms may be worthless in control of carriers and those showing vague intestinal symptoms from the organisms, while on the other hand drugs useful in treatment of the carriers may be valueless in

control of the acute symptoms. We must, therefore, bear in mind that the disappearance of symptoms does not necessarily mean the cure of the infection, but as in syphilis, the organism is merely arrested in its activities. If we look at the infection in this manner, physicians would be on the out-look for exacerbations of the disease, and a person once injected and treated would be kept under observation as we do with syphiletics.

Since we have no definite routine to follow and no drugs which have been proven to be specific, we must consider and discuss the value of various drugs which have been advocated and used in the past. Some authors state that there are drugs which are specific for the treatment of the disease; however, this is only true in their hands, and the specificity of these drugs has proven doubtful in several cases. However, we do know that there are certain drugs that will control the acute symptoms of the disease and some which if properly administered will cause the disappearance of *Entameba Histolytica* from the stools of infected individuals; but such individuals thusly cured have been subject to relapses. It has, therefore, been found necessary to employ drugs which will not only arrest the organism in its activities, but prevent its recurrence. Therefore, drugs used in the past with favorable results will be discussed as to their value, toxicity, etc.

IPECACUANHA: This was used in the treatment of dysenteries in India as early as 1600, according to Rogers (111).

The efficiency of the drug depends upon its content of alkaloids, the principal ones being emetine and cephaeline; of these, emetine has repeatedly shown its superior value in the treatment of amebic dysentery

and amebiasis. Ipecacuanha possesses all the virtues of emetine in the treatment of amebic dysentery, with the added amebicidal action of cephaeline, but owing to the difficulties encountered in administration it is used very little today. However, in stubborn cases which resist other forms of treatment, it is certainly worthy of trial.

Simons (112) urged the use of the drug in salol coated capsules in 1909 to replace the powdered root. Dock (113) in 1909 also advocated this method of administration. Simons' method of treatment is as follows: Bed rest for a period of approximately two weeks; liquid diet without milk, and a mild laxative before beginning the course of treatment.

The pills, as stated above, should be coated with salol and contain powdered ipecacuanha of 5 grains each, and should be administered at night just before retiring; two or three hours after a meal. Ten to fifteen pills are to be given at a time to get the desired effect, and should not be given during the day in divided doses. The full treatment consists of 100 pills or the equivalent of 500 grains of the powdered root. The stools should be watched for undissolved pills and in case any pass through, the number lost should be repeated in order that the total dosage be sufficient. Simons states that with this method of treatment he has had very few relapses, but that he does not use it now except in infections which have proven resistant to other forms of treatment.

The drug has nauseating effects and is therefore difficult to administer. It also has toxic effects since it contains a considerable quantity of emetine.

EMETINE: In 1817 Pelletier (114) described an alkaloid in ipecacuanha which he called emetine. The amebicidal activity of emetine was demonstrated in 1912 by Vedder (115). Rogers (116) in 1912, following Vedder's suggestion, used emetine in treatment of amebiasis and amebic dysentery with good results. However, Vedder states in his article that emetine was employed in the treatment of diarrheas and dysentery as far back as 1829.

The salt used in medicine is the hydrochloride, because of its greater solubility, and is used by subcutaneous or intra-muscular injections, because it does not produce as much nausea and vomiting when used in this manner. There is no indication whatsoever to administer emetine hydrochloride intravenously.

Emetine has an accumulative action and toxic symptoms are frequently noted following its administration. The pathological picture shows it to be a protoplasmic poison; its action being chiefly on the heart muscle, but it may involve other muscles as well. The toxic symptoms which have been observed in emetine poisoning are sudden cardiac failure, myocarditis; wrist, ankle or toe drop; muscular pain and weakness; cardiac arrhythmias; nausea and vomiting, and great prostration. Thus, it is the consensus of opinion that the drug should be employed with great caution, especially if the patient has, or has had, heart or kidney diseases.

The dosage is 1 grain subcutaneously or intramuscularly per day, or less, and not more than 12 grains should be administered in a course of treatment and the treatment should not be repeated within a month's time. Most authors discourage its use in children unless other less toxic drugs have failed.

The drug has a direct action on the amebae; a dilution of 1:25,000 killing and amebae and a 1:50,000 dilution inhibiting growth (117)-(118). St. John (119) confirms this by observing the lethal effect of emetine upon *Entameba Histolytica* in a concentration of 1:5,000,000. Thus, we see that the amebae are readily destroyed, but so many patients have relapses following a thorough course of treatment. This is significant and since this drug has accumulative action, most authors agree that it should be used only in acute cases and the amount given should never exceed 12 grains during a course of treatment. A routine method of treatment will be discussed later.

EMETINE BISMUTH-IODIDE: Was first introduced by DuMez (120) in the Philippine Islands in 1915. This drug contains 29% emetine; 12% bismuth and 58% iodine.

The favorable use of the drug was later reported by Low and Dale (121) in 1916 and by Dobell (122) the same year in the treatment of carriers or individuals proving resistant to emetine hydrochloride.

However, the toxicity of this preparation has been found to be the same as emetine if sufficient quantities of the drug are administered.

The dosage is 3 grains once a day for twelve consecutive days. The patient must be placed in bed during the course of the treatment. If the dysenteric symptoms are very severe, it is recommended that one or two doses of emetine hydrochloride be given subcutaneously and followed by a routine course of emetine bismuth Iodide.

The drug may be administered in gelatine coated capsules only, because of its nauseating effects. It is usually given at night after meals, with a cup of hot tea or broth, while the patient is flat in bed. Nausea and vomiting nearly always occur, but usually lasting only one or two days. The patient should remain in bed throughout the entire treatment and should be warned about over-exertion for two to three weeks after the course of treatment. During the treatment the pulse should be watched very closely and treatment discontinued if there is any marked reduction or frequency or strength of the pulse, or if any form of arrhythmia develops.

The action of the drug is thought to have a higher curative value than emetine. This factor being due to the iodine content. However, the drug must be properly administered to obtain the desired effect, and then we encounter difficulties because of the unpleasant symptoms produced by the drug. It is common belief today that we possess other and better drugs. Therefore emetine bismuth iodide is considered to be of little value in the therapy of amebiasis (123).

ACETARSONNE: Also known as Stovarsol, which is an arsenical preparation. This drug has been used quite extensively in the treatment of amebiasis, especially in the treatment of carriers and convalescents, and with surprisingly excellent results in eliminating amebic infection.

The toxicity of this drug is unfortunately high because of its arsenic content and because of the cumulative action of the arsenic. For this reason, symptoms of arsenic intolerance such as colic,

puffiness of the face and eyelids, fever, erythematous eruptions, i. e., on the fore-arms, should be watched for by the physician when employing the drug.

The dosage was formerly recommended as 4 grains three times a day for seven days; cessation of treatment for one week and then continuing with 4 grains three times a day for another seven days. However, recent investigations have found that the dose could be reduced to half the amount and favorable results could be obtained with very few individuals showing toxic symptoms (124).

The drug is now recommended to be administered by mouth in dosages of 2 grains instead of 4, and following the same outlined treatment.

Since the drug can be administered without interfering with the occupation of the patient, it can be used in the treatment of carriers and those with mild symptoms of amebiasis. However, it is not advocated for the treatment of acute symptoms or in the treatment of individuals who cannot report to the physician for frequent observation.

TREPARSOL: This drug is also an arsenical preparation which is supposedly less toxic than acetarsone. Brown (125) of the Mayo clinic strongly advocates its use in conjunction with emetine hydrochloride.

The dose as recommended by him is 4 grains three times a day with meals for a period of four days, cessation of treatment for ten days; then 4 grains three times a day for four days, no treatment for ten days, and repeat the 4 grains three times a day for another period of four days. The tablets should be chewed with the food as

this causes a greater dispersion of the arsenic; in this way the drug is more rapidly excreted in the urine and therefore does not have so much cumulative action. Brown states that the indiscriminate usage of the drug is not without risk; however, since it is rapidly excreted by the urine it would be preferable to acetarsone. In his hands he obtained cures in 89% of 46 patients treated in this manner.

CARBARSONE; ^{Carbarzone} Which is another arsenical compound introduced by Anderson and Reed (126) in 1931. They find that the drug is excreted in the urine about the same rate as acetarsone, but by them it was found to be less toxic and also to have a therapeutic index eight times as great.

The toxicity is very low. They have administered the drug to 330 patients in total doses ranging from 75 to 2,100 mg. per kilo in divided amounts over as long as fifteen months, with a single instance only of intolerance in a patient with acute hepatitis. They state that slight gastric distress has been noted, but no evidence of injury to the kidneys, skin, optic nerve or other tissues has been observed to date. From this, it is quite evident that carbarzone is much less toxic than other arsenicals and should be used in preference to them.

The dosage recommended is 4 grains twice a day for ten days, which may be repeated in ten days in resistant cases. It may be administered rectally as a retention enema daily for five days, with 200 cc. of 2% sodium bicarbonate containing 1% carbarzone.

The action, of course, is due to the arsenic content.

This drug has been found to be the most valuable of arsenical preparations for the treatment of amebiasis. However, it should not be given if there is evidence of heart, liver or kidney disease.

CHINIOFON: Also sold under the names of yatren and anayodin.

The drug is a sodium-iodoxyquinolinsulphonate and contains 26% to 28% iodine, supplied incoated or uncoated tablets of 4 grains each. The drug was introduced in the treatment of amebiasis by Muhlens and Menk (127) in 1921. There has been considerable literature published since the drug was introduced and has proven it to be a very efficient amebicide, and the drug is practically free of toxic properties when employed in therapeutic doses. This factor has repeatedly been proven by authentic sources. However, in many individuals where a full dose is given, a more or less profuse diarrhea may occur, usually lasting two to three days, but is rarely severe and will disappear immediately on cessation of the drug.

This drug seems to be one of the most efficient in treatment of convalescents and carriers. However, in some cases it, along with several others, may fail to be curative, but is strongly advocated in treatment of the malady today. The effectiveness of the drug is due to the direct action of the iodine content on the organisms (128).

VIOFORM: Which chemically contains 37.5% to 41.5% iodine and 11.5% to 12.2% chlorine. It was favorably introduced as an amebicide in 1933 by David, Johnstone, Reed and Leake (129).

Its toxicity is very slight unless the therapeutic dose is exceeded. If toxic symptoms do occur they subside immediately with

cessation of the drug.

The recommended dosage is 4 grains three times a day for ten days, an interval of one week without treatment and then repeat the above dosage for ten days. The# men who introduced the drug claim that such a course of treatment will free the stools of the organisms in an average case of amebic dysentery.

The drug is given by mouth in gelatine coated capsules. It is not recommended to be used rectally because of its irritant action upon the mucous membrane of the intestine, and should not be given intravenously since it is apt to produce toxic symptoms this way and it is no more efficient than when administered by mouth.

The destructive action of vioform on the organism is due to its iodine content, as in chiniofon. It has been used very successfully by its advocates and is supported by other men who have had experience with chiniofon.

Numerous other drugs have been advocated and used by different men, such as Kurchi bark, which has been practically abandoned except in India where it is grown, because of its expense. The drug has no advantages over the cheaper drugs that have been advocated. If one so desires to investigate the various drugs that have been advocated and used, I refer you to Craig's recent work on amebic dysentery (130).

OIL OF CHEMOPODIUM: Has long been known to be an effective anthelmintic. There is very little literature on its use in amebic dysentery or balantidal dysentery, but during a recent interview with Dr. C. W. Mason (131) I find that he had had amazing results with its

use, and the drug has been so successful in his hands that he considers it almost specific for the organism and believes it to be worthy of trial in similar forms of dysentery.

He advises giving 4cc of the oil in 30cc of olive oil as a retention enema, instructing the patient to retain the enema as long as possible. He states that he has treated hundreds of cases of dysentery in this manner, in the stools of which he was able to demonstrate *Entamoeba histolytica*, and has rarely been able to demonstrate the organism in the stools after one application and never after two such applications. Since this drug has proven to be so successful in his hands, it certainly is worthy of further application.

The drug is known to have toxic symptoms, but only in large quantities. Cort (132) following Mason's suggestion treated a case of balantidial dysentery with the oil, but used a dosage of 15cc to 150cc of olive oil. The enema was retained for three and one-half hours without any toxic symptoms. He did, however, encounter some toxic symptoms due to an error on the part of an interne in which the patient received two enemas, each containing 15cc of the oil, within twenty-four hours. About two hours after the second enema was given, the patient was in an immediate state of collapse with profuse vomiting, extreme weakness and vertigo. He immediately received normal saline enemas and within a few hours seemed normal with the exception of impaired hearing, which cleared up in a few months. It is Mason's belief that toxic symptoms would not have occurred in this case had the advocated dosage been used. He advocates the use of oil of chenopodium in acute as well as in the chronic and so-called carrier

stages of the disease.

Since we have found not a single drug or method of treatment that will eliminate the infection in every case of amebic dysentery, an outline of the most effective method of treatment will be discussed.

ACUTE AMEBIC DYSENTERY: As previously mentioned, general prophylaxis is essential in control of the disease. However, after having been infected with the organism and the typical symptoms produced, one must resort to the measures by which the patient can be relieved of symptoms and elimination of the organism.

In the acute stages it is essential to confine the patient to bed on a liquid or soft diet; preferably liquids.

Emetine hydrochloride seems to be our most valuable drug in the treatment of the acute stages of amebic dysentery. However, it is employed only to control the acute symptoms, because past experience has taught us that it is not capable of curing the disease.

Craig (133) advocates giving emetine hydrochloride subcutaneously in doses not to exceed 1 grain (.065 gm.) daily until the dysenteric symptoms subside and the stools become semi-formed or formed, and this daily dose should not be given for more than 12 days. After the symptoms have subsided, chiniofon is employed. The drug is given by mouth in gelatine coated pills containing 4 grains each; the usual dosage being 2 to 4 pills three times daily for ten days, and may be repeated within ten days if necessary.

In most cases the acute dysenteric symptoms will

subside in from four to eight days after beginning this method of treatment. According to Craig's experience it is unusual to have to continue the treatment for a full twelve days.

While the patient is receiving emetine, the physician should watch closely for symptoms of intolerance, since the drug has a cumulative action and is not free from toxic symptoms. In too large doses it may cause a severe diarrhea, myocarditis, nervous prostration and great muscular weakness. Death may occur suddenly from cardiac failure. If such symptoms should develop, administration of the drug should be discontinued immediately. The symptoms of intolerance will as a rule clear up within a few days. The drug should never be given intravenously.

If there are contra-indications, as heart or kidney diseases, to the use of emetine, chiniofon may be used alone. It is administered in larger doses than previously described, using 7.5 grains three times a day for eight to ten days, and may be repeated in ten days. A diarrhea may develop or become more severe if too large doses are used. However, if such is the case the dosage may be cut down. The diarrheal symptoms usually last only two or three days. It is also good therapeutics to administer daily enemas of 200cc of 2% warm water solution of chinifon with advice to the patient to retain the emema as long as possible.

The treatment is governed by stool examinations. A microscopic examination of the stool should be made following each course of treatment and if the organism is still present, a routine course of treatment should follow. At least three negative stool examination, one week apart, before the patient may be considered

acured, and thereafter at least one stool examination a month for the next six months with negative reports. If either vegetative or cystic forms of the organism are observed during this time, the routine course of treatment should be repeated.

If the treatment thus recommended fails to eliminate the infection, even though the symptoms may disappear, which will according to Craig (134) be infrequent, one should employ other amebicidal drugs, as carbarsone and vioform. It is much better according to most observers to employ other amebicidal drugs rather than repeated series of one special remedy. As it has been previously stated, no one drug is specific in every case, and it would be folly to adhere to any one drug after it had proven itself unable to eliminate the infection.

CHRONIC AND CONVALESCENT AMEBIC DYSENTERY: The treatment of the more chronic forms of the disease will depend on whether or not the patient was seen during an acute exacerbation of the dysenteric symptoms or between attacks. If during the exacerbative stage, he should receive the treatment outlined for acute amebic dysentery, but however, if the patient is of the latter type he should be considered as a carrier of the organism. Craig (135) has shown chiniofon to be the most efficient and the safest drug in treatment of the so-called carriers, with or without symptoms.

He advises giving three to four pills of chiniofon three times daily for a period of ten days, and this may be repeated if deemed advisable. If diarrhea should develop, it usually lasts for two days or less and should not be considered as an indication for cessation of the treatment, unless it becomes too severe. In fact,

it is the common belief that the diarrhea aids in the process of eliminating the organism.

The drug may be administered without interfering with the patient's daily routine and no precautions are necessary regarding the diet, etc., although one should avoid those foods which are apt to cause distention and irritation of the bowel. Chiniofon when given to children should be administered in doses proportional to the age. Reed (136) and several others have reported the favorable use of this drug both in treatment of carriers and in conjunction with emetine in the more acute cases.

Other drugs have been employed in the treatment of convalescents and carriers; as the arsenical preparations of treparsol, acetarsone, carbarsone. But, owing to the danger of arsenic poisonings; these drugs, while quite efficient, should not be employed unless the less toxic drugs have failed to eliminate the infection.

The results of treatment of carriers of *Entameba Histolytica* should be governed by frequent examinations of the stools. The stools should be examined, following a completion of a course of treatment, at least once a week for three consecutive weeks, and once thereafter for three consecutive months. If the organism is still present after treatment, another course of treatment should follow within one week's time.

TREATMENT OF COMPLICATIONS

AMEBIC ABSCESS OF THE LIVER: This is in itself largely a surgical problem, but early recognition and treatment of amebic hepatitis is essentially a medical problem. Rogers (137) and several others have repeatedly shown that there is a period during evolution of an amebic abscess of the liver in which more or less characteristic symptoms may be recognized and early instigation of treatment may abort the formation of an abscess.

The occurrence of leucocytosis, fever and discomfort or pain in the hepatic region in patients suffering from intestinal amebiasis, is almost diagnostic of amebic hepatitis. Rogers was first to advocate immediate administration of emetine, and his method of treatment has been repeated confirmed by latter observations.

Emetine hydrochloride should be given subcutaneously in 1 grain doses daily, for a period of twelve days or less. Under this regime the fever should disappear within one week and there should be a marked drop in the leucocytosis or a return to normal white blood count. If the fever continues longer than this, it is evitable that suppuration has occurred and should possible be treated surgically. However, Rogers has demonstrated that even large liver abscess may be cured under the above described treatment.

Cassoni (138) also believes that emetine is specific in treatment of amebiasis of the liver and that surgical intervention is

unnecessary unless there is amixed infection or perforation has occurred into the surrounding viscera.

While on the other hand several authors believe that more rapid progress is made by surgical aspiration after five or six injections of emetine hydrochloride have been given and the fever is normal. Since the specificity of emetine has been discovered, open operationfor amebic hepatitis is obsolete and is not advised unless secondary infection and suppuration has occurred, or perforation of the amebic abscess into adjacent viscera (139).

Surgical intervention, however, should not be attempteduntil emetine has been given adequate time. These patients should also receive a course of treatment as advised for treatment of carriers.

TREATMENT OF OTHER COMPLICATIONS: Lung abscess, the third most common site of amebiasis, is seldom diagnosed and is therefore seldom treated. After having made the diagnosis, one should administer a routine course of emetine as described in treatment of amebiasis of the liver. In some cases surgical intervention may be necessary, but very rarely, because the condition is not commonly diagnosed ~~except at~~ autopsy.

Abscess of the brain should be treated medically and surgically. A routine course of emetine hydrochloride is given, accompanied by surgical drainage. However, to date surgical treatment is of little value, because of the grave prognosis that the complication carries with it.

General peritonitis or perforation of the intestine

by an amebic lesion demands immediate operation, general therapeutic measures for peritonitis, and routine course of emetine. Amebic peritonitis carries with it a very high mortality.

Acute appendicitis due to amebae should be treated with emetine hydrochloride and chiniofon, and by all means should not be operated until the effects of these drugs have been ascertained. Even then one should proceed with caution, because few operations are successful since the caecum is nearly always involved.

At the present time one seldom observes the complications of fifty years ago, because of the additional knowledge, recognition and therapeutic measures of the disease. As time marches on, the physician should be sufficiently trained to recognize the disease and to instigate treatment early enough to prevent the spread of the disease and to prevent the occasional disastrous complications.

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