THE ETIOLOGY, DIAGNOSIS, AND TREATMENT OF AMEBIASIS

BY

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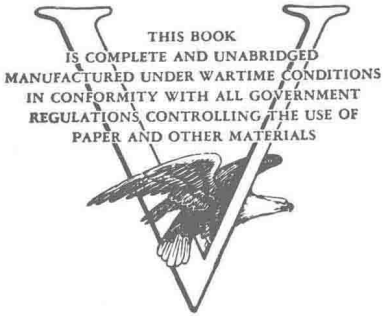

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PREFACE

In 1934, the writer published his work entitled: "Amebiasis and Amebic Dysentery," which included the salient data available to that date upon this important subject. During the past decade, since that work was published, an enormous amount of research has been accomplished upon almost every phase of amebiasis and in this new book upon the subject it has been the writer's aim to include all the important data accumulated during this period, adding it to the material published in the previous work.

Despite the many publications upon amebiasis that have appeared during the past decade there is a surprising amount of ignorance regarding this infection among many physicians, as evidenced by the letters received by the writer requesting information upon various phases of the subject. This has been due, as in the past, to the general belief that amebaisis is a tropical infection, of little interest to physicians in temperate regions, a belief that is very erroneous and harmful. At the present time, thousands of our troops are serving in regions where amebiasis is a common and often serious infection, and many of these men will return to the United States infected with *Endamoeba histolytica*, the cause of amebiasis. This will add to the already considerable percentage of infections with this parasite in this country, conservatively estimated at 10 per cent of the population, and will render the diagnosis and proper treatment of the infection of still greater importance from the standpoint of public health. For this reason the writer believes that this book should prove of value to the general practioner, public health official, and medical officers of the Army, Navy and Public Health Service, as he had endeavored to include in it all of the data of value now available regarding amebiasis.

It is obvious that in preparing this book the writer is indebted to the publications of the many authorities who have contributed to our knowledge of amebiasis and he has tried to give credit where due and his thanks are here expressed to all those who have given him such data or helped him in any way in the preparation of this volume. A reference list of the most important contributions to the subject will be found at the end of the volume and also a list of authorities. In the text it will be noted that following the name of each authority mentioned there is included in parentheses the date of that authority's publication, and in order to use the reference list all that is necessary is to find in the list the name of the authority and the corresponding date as given in the text.

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CHARLES F. CRAIG.

San Antonio 1, Texas
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Chapter I

INTRODUCTION

Definition of Amebiasis and Amebic Dysentery. History. Geographical Distribution.

Definitions

The clinical term "amebiasis" includes all conditions caused by the invasion of the tissues of man by the pathogenic ameba known as *Endamoeba histolytica*. The invasion of the various tissues of the body occurs primarily through the mucous membrane of the large intestine and less often through that of the lower portion of the ileum. The symptoms of such invasion vary from slight disturbances of the digestive system to the most severe symptoms of dysentery, amebic abscess of the liver and other organs, and complicating symptoms caused by a secondary invasion of the tissues by bacteria derived from the intestinal tract.

The term "amebic dysentery," formerly used to indicate all infections with *Endamoeba histolytica*, with the exception of amebic abscesses of various organs, is now properly restricted to infections in which the prominent symptom is a bloody diarrhea induced by this parasite. Even to-day, a few texts still retain the term "amebic dysentery" in describing amebiasis but fortunately the vast majority of modern authors describe infection with this ameba under the general term "amebiasis."

In 1927, the writer stated: "It is most unfortunate that the term 'amebic dysentery' should have become in the minds of most medical men, a synonym of amebiasis, or amebic infection; for while dysenteric symptoms are quite characteristic of the serious infections with *Endamoeba histolytica*, the vast majority of such infections are not accompanied by dysenteric symptoms but by much milder symptoms usually attributed to some other factor and not recognized as the result of infection with this parasite." This general use of the term "amebic dysentery" was caused largely by the fact that amebic infection was considered of tropical origin and in the tropics dysentery is very frequently one of the symptoms of amebiasis." The recognition of the fact that amebic dysentery is but a small part of the clinical picture of amebiasis is essential to any intelligent understanding of infections with *Endamoeba histolytica* and it is most encouraging to note that almost all modern writers have abandoned the term "amebic dysentery" in describing such infections and have adopted the general term "amebiasis" as recommended by the writer many years ago.

History

The history of amebiasis and amebic dysentery begins with the discovery by Lösch, in 1875, of the pathogenic ameba now known as *Endamoeba histolytica*, but which he named "*Amoeba coli*." Whether other observers had seen this ameba prior to Lösch remains questionable. Both Lewis (1870). and Cunningham (1871) described amebae in the stools of patients suffering from cholera in India which are generally considered as being identical with the harmless ameba, *Endamoeba coli*, but it is certainly possible that they may have seen the pathogenic ameba and were unable to differentiate it from the harmless species. At any rate, it is believed that to Lösch belongs the credit for the discovery of the pathogenic species and that to him we owe our first knowledge of amebic dysentery.

In 1875, Lösch, while examining the stools of a patient suffering from a relapsing type of dysentery in St. Petersburg, Russia, found motile amebae present, many of them containing red blood corpuscles. From his description it is evident that he was dealing with *Endamoeba histolytica* and an autopsy upon the patient revealed marked ulceration of the large intestine and numerous motile amebae were found in the material obtained from the ulcers. Lösch endeavored to produce dysentery in 4 dogs by feeding and the rectal injection of stools containing the motile amebae, and was successful in one animal which developed dysentery with motile amebae in the exudate, while at autopsy its large intestine was found ulcerated and motile amebae were obtained from the ulcers and the intestinal contents. Despite the evidence furnished by this successful experiment, Lösch did not regard the amebae as the cause of the dysentery but suggested that the presence of these parasites might delay or prevent the healing of the ulcerations which were present. He named the ameba, *Amoeba coli*, a name by which it was known until Schaudinn's observations were published in 1903.

Koch, in 1883, observed 5 cases of dysentery in Egypt, 2 of them complicated with abscess of the liver, and in the ulcers occurring in the large intestine he found numerous amebae and in sections these were also found deep in the tissues at the base of the ulcerations, as well as in the capillaries of the liver, close to the abscess walls. Koch considered that because of the location in the tissues they bore some relation to the disease.

In 1886, Kartulis published a paper describing his results in the study of 150 cases of dysentery in Egypt in all of which he demonstrated amebae identical with those described by Lösch. In sections of the diseased intestine in 12 cases he found the amebae in the ulcers and the tissue beneath the ulcers, and he states that he believes that these amebae were the cause of "tropical dysentery," which he considered to be the form of the disease which he studied. In 1887, Kartulis published another paper in which he stated that he had found the same ameba in the pus of liver abscesses and

that this ameba was the cause of the liver abscesses so frequently observed in the tropics as a sequella of dysentery, while in 1904 he published his discovery of the same ameba in abscess of the brain following dysentery. Kartulis was also successful in producing dysentery in cats by rectal injection of feces containing amebae and the contributions of this authority to our knowledge of amebiasis and amebic dysentery will always rank as among the most important that have been published on the subject.

Shortly after the publication of the first paper by Kartulis an investigation of cases of dysentery occurring in Prague by Hlava (1887) resulted in his finding the ameba in 60 cases of the disease and he was successful in causing dysentery in 2 of 17 dogs and in 4 of 6 cats by the rectal injection of feces containing motile amebae from human cases.

The first observer to demonstrate amebae in a case of dysentery in the United States was Osler, who, in 1890, found amebae in the stools of a patient suffering from dysentery and abscess of the liver, and his observations were followed in the same year by those of Stengel (1890), and in 1891, by those of Musser and Dock, who also demonstrated the ameba in cases of dysentery in this country.

Stimulated by the observations of Osler, Councilman and LaFleur studied 14 cases of amebic dysentery observed at the Johns Hopkins Hospital, and in 1891 published a monograph upon amebic dysentery which has always remained a classic upon the subject. In this work they concluded that amebic dysentery is a clinical entity and that it is characterized by definite pathologic lesions produced by the amebae. They were the first to use the terms "amebic dysentery" and "amebic abscess of the liver", and they suggested the name "Amoeba dysenteriae" for the parasite. To the work of these authors may be credited the awakening of interest in this subject among American physicians.

In 1892, Kovacs was successful in producing dysentery in 5 kittens with amebae from human dysentery cases and in 1894, Kruse and Pasquale produced typical amebic dysentery in a cat by the rectal injection of bacteriologically sterile pus from a liver abscess containing amebae, thus demonstrating beyond doubt that the amebae, and not bacteria, were the cause of the disease.

In 1893, Quincke and Roos published their researches upon the ameba found in amebic dysentery cases, followed by a publication by Roos, in 1894. These observers gave a very clear description of *Endamoeba histolytica* and were the first to describe the cysts of this parasite. In addition, they studied amebae occurring in patients not suffering from dysentery and clearly differentiated the pathogenic species from the amebae occurring in healthy individuals and those suffering from diseases other than dysentery. Unfortunately, Quincke and Roos failed to study closely the

morphology of the motile and encysted forms of *Endamoeba histolytica*, especially as regards the number and structure of the nuclei in the cysts, and it remained for Huber (1903) to give the first accurate description of the cysts of this parasite. Huber determined that the cysts of *Endamoeba histolytica* contained from 1 to 4 nuclei and he was able to infect cats by feeding them material containing the cysts and by the rectal injection of the motile forms, or trophozoites.

In 1900, Strong, in the Philippine Islands, demonstrated that the prevailing types of dysentery in those islands were amebic and bacillary dysentery and differentiated the pathogenic from non-pathogenic amebae occurring in the human intestine by experiments on cats, finding that the pathogenic ameba, which he called *Amoeba dysenteriae*, produced typical ulcerative lesions in these animals, while the non-pathogenic ameba, *Amoeba coli*, as well as free-living amebae cultivated in straw infusions, produced no lesions in these animals. This work long antedated that of Walker and Sellards (1913) and to this observer belongs the credit of first offering scientific proof of the existence of pathogenic and non-pathogenic species of amebae in man.

In the same year that Huber published his work there appeared a contribution by Schaudinn (1903) in which Huber's observations as to the cysts of *Endamoeba histolytica* were disregarded, and an erroneous method of reproduction by spore formation, or budding, was described. This description of the life cycle of the parasite was accepted by numerous workers upon the subject and resulted in the observations of Quincke and Roos and of Huber regarding the cysts being ignored or forgotten, so that in 1907, Viereck redescribed these cysts and believed them to be those of a new species of ameba, while Hartmann (1908) also redescribed them and considered them the cysts of a new species of ameba which he called *Entamoeba tetragena*. This supposed new species was confirmed by numerous investigators but Walker (1911) conclusively demonstrated that *Entamoeba tetragena* is identical with *Endamoeba histolytica* and his conclusions have been accepted by all students of the parasitic amebae.

The first observer to produce an abscess of the liver in an experimental animal after the production of dysentery by the rectal injection of *Endamoeba histolytica* was Harris (1901), who infected puppies with this parasite with the production of amebic dysentery and the subsequent development, in two of the animals, of amebic abscess of the liver. Later amebic abscess of the liver was produced in this manner in cats by Craig (1905), Huber (1909), Wenyon (1912), Baetjer and Sellards (1914), and Dale and Dobell (1917).

During the period from 1879 to 1901 the following facts had been established regarding the relationship of *Endamoeba histolytica* to dysentery and abscess of the liver:

1. That amebae identical in morphology with the ameba described by Lösch occurred in the feces and intestinal lesions of patients suffering from a clinical form of dysentery known as amebic dysentery, and in the sterile pus from liver abscesses occurring as a complication of this form of dysentery.

2. That the rectal injection and feeding of feces containing these amebae in cats and puppies resulted in the production of dysentery in these animals accompanied by pathological lesions similar to those observed in amebic dysentery in man.

3. That the rectal injection of amebae in the otherwise sterile pus of amebic abscess of the liver into cats produced dysentery in the experimental animals.

4. That the feeding of puppies with the cysts, or the rectal injection of these animals with the trophozoites of *Endamoeba histolytica* sometimes resulted in the production of amebic abscess of the liver subsequent to the occurrence of amebic dysentery in such animals.

5. That two species of amebae occurred in the human intestine, one pathogenic and the other, non-pathogenic.

The results of all these observations appeared to be sufficient to prove that the ameba first described by Lösch was the cause of amebic dysentery and the peculiar form of liver abscess associated with the disease, but the fact that amebae also occurred in the feces of healthy individuals, and those suffering from many other diseases, caused much confusion and the refusal of many authorities to accept the ameba of Lösch as the etiological factor in dysentery or liver abscess. Among the first to explain this apparent difficulty may be mentioned Councilman and Lafleur (1891) who, in their monograph upon amebic dysentery, definitely stated that they believed that both pathogenic and non-pathogenic species of amebae inhabit the intestine of man, while Quincke and Roos (1893) described the chief morphological distinctions between the pathogenic ameba now known as *Endamoeba histolytica* and the common non-pathogenic species now known as *Endamoeba coli*, and Strong (1901) demonstrated by experiments on cats the pathogenicity of the former species and lack of pathogenicity of the latter. However, these contributions were overlooked and it was not until Schaudinn (1903) published his researches upon amebic dysentery, that it became generally accepted that a pathogenic and non-pathogenic species of ameba were parasitic in the human intestine. Schaudinn gave good descriptions of the trophozoites of the two species but overlooked the cysts of the pathogenic species, as already noted. In ignorance of the genus *Endamoeba* established by Leidy, in 1879, to include a parsitic ameba of the cockroach, he placed the two amebae of man in the genus *Entamoeba*, established by Casagrandi and Barbagallo, in 1895 and gave the name *Entamoeba histolytica* to the pathogenic species and the name *Entamoeba coli*

to the non-pathogenic species. While Schaudinn gave a very erroneous account of the method of reproduction of *Endamoeba histolytica* and entirely missed observing the cysts of this parasite, his work must be admitted to be among the most important accomplished upon the subject. The observations of Schaudinn were confirmed, either in whole or in part, within the next few years by several investigators. The first confirmatory report was published by the writer, in 1905, in which the diagnostic differences between *Endamoeba histolytica* and *Endamoeba coli* were clearly described and it was demonstrated by experiments upon kittens that the former species was pathogenic and the latter, non-pathogenic. The writer was able by both feeding and rectal injection of material containing *Endamoeba histolytica* to produce dysentery in young kittens and in one animal an amebic liver abscess occurred as a complication of the dysenteric process. On the other hand, all of the writer's experiments in feeding and the rectal injection of material containing *Endamoeba coli* gave absolutely negative results. This contribution was followed by those of Werner (1908) and Hartmann (1909), but the final proof of the existence of these two species of ameba was not furnished until the work of Walker and Sellards (1913), who demonstrated the pathogenicity of *Endamoeba histolytica* and the non-pathogenicity of *Endamoeba coli* by feeding human volunteers with material containing the cysts of these two parasites. The work of Walker and Sellards is discussed later.

Since the publications referred to above still other species of amebae have been found parasitic in the human intestine and their presence add difficulty to the differential diagnosis of the pathogenic species, as all of these other species are harmless, so far as is known. Prowazek (1911–1912) described an ameba occurring in the intestine of man which he named *Entamoeba williamsi* and which Dobell (1919) placed in a new genus, *Iodamoeba*, naming it *Iodamoeba bütschlii*, the name by which it is most widely known. In 1917, Wenyon and O'Connor described another species of ameba found in the human intestine, naming it *Entamoeba nana*. This ameba was afterward placed in the new genus *Endolimax* by Kuenen and Swellengrebel (1917) while Brug, in 1918, named it *Endolimax nana*, the name by which it is now generally known. In 1918, Jepps and Dobell described still another species of ameba living in the intestine of man and named it *Dientamoeba fragilis*. All of these species are harmless commensals in the human intestine and are of importance only in that they must be differentiated from the pathogenic species, *Endamoeba histolytica*, and add much to the difficulty of diagnosis.

The *cultivation of Endamoeba histolytica* upon artificial culture media *in vitro* was probably first definitely accomplished by Cutler (1918) but his observations were not confirmed and to Boeck and Drbohlav (1924–1925)

belongs the credit of first cultivating this parasite upon a medium which can be prepared without difficulty and upon which the amebae can be cultivated indefinitely with suitable precautions. These investigators proved conclusively that *Endamoeba histolytica* can be cultivated and that the cultures of this parasite are pathogenic to kittens, producing in these animals the intestinal lesions characteristic of amebic dysentery in kittens. Strains of the parasite may be maintained in media for months and the writer maintained a strain for over five years which, at the end of this period, was still pathogenic for kittens. Numerous investigators have confirmed the cultivation work of Boeck and Drbohlav and many media have been evolved upon which this parasite will develop, and cultivation methods are successfully used in the diagnosis of this infection.

Recent contributions have added greatly to our knowledge of the biology of *Endamoeba histolytica* and will be considered later. The serology of amebiasis has been studied by many observers and it has been demonstrated that complement fixing bodies are present in the blood of individuals infected with *Endamoeba histolytica* by Izar (1914), Scalas (1921), Craig (1927), Menendez (1932), Heathman (1932), Sherwood and Heathman (1932), Spector (1932), Tsuchiya (1932), Weiss and Arnold (1934), Stone (1935) and many more recent workers. The writer, in 1927, demonstrated the presence of hemolytic and cytolytic substances in extracts of cultures of *Endamoeba histolytica* which were not of bacterial origin but evidently secreted by the ameba and in 1929, described the technique of a complement fixation test which has proven very useful in the diagnosis of amebiasis.

The modern clinical conception of amebiasis as distinguished from the phase known as "amebic dysentery" has been of gradual growth and little had been written upon the subject prior to a paper by the writer, published in 1921, calling attention to the fact that amebic dysentery is, in this country, a comparatively rare condition, but that diarrheas and other symptoms of gastro-intestinal irritation were very commonly caused by *Endamoeba histolytica*, even in presumably healthy "carriers" of this parasite. This contribution stimulated much interest in the subject and to-day it is recognized by all well informed physicians that amebiasis is responsible for many clinical symptoms far different from those of acute or chronic amebic dysentery. The recognition of the true character of amebiasis has been a great step in advance in its history and has lead to the institution of proper methods of prophylaxis and treatment.

Geographical Distribution

The geographical distribution of amebiasis is probably world-wide, for wherever infection with *Endamoeba histolytica* has been looked for it has been found. As will be noted later, infections are more numerous in the

tropics and subtropics, but in poorly sanitated districts in temperate and cold countries the incidence of infection may be very high, almost as high as in similar localities in warm countries. This subject will be fully considered in the discussion of the epidemiology of amebiasis but it may be stated here that this infection is wide-spread throughout the United States and it has been conservatively estimated that from 5 to 10 per cent of the population of this country is infected with *Endamoeba histolytica* and it is the writer's belief that at least 50 per cent of individuals infected with this parasite have definite symptoms which are caused by its presence.

While amebiasis has a world-wide distribution the severe lesions and symptoms which are present in amebic dysentery occur much more frequently in the tropics and the warmer portions of the sub-tropics than in temperate and cold climates. Amebic dysentery has long been known to be very prevalent in certain tropical countries and for this reason it has usually been considered as a tropical disease, but no conception could be further from the truth, for amebic dysentery does occur in temperate regions and much more frequently than is generally believed.

In Europe amebic dysentery occurs sporadically in practically every country but is common in Russia, Galicia, Poland, Spain, Malta, Sardinia, Turkey, Greece and Italy, especially among the poorer classes living in poorly sanitated localities. In Asia it is most prevalent in India, Mesopotamia, Palestine, Syria, China (especially the southern part), the East Indies, Cochin China, Siam, the Malay States, Formosa and Korea and Japan. It was very prevalent in the Philippine Islands under the Spanish regime and was one of the most deadly diseases affecting American troops operating in these islands during the Philippine Insurrection. Sporadic cases of amebic dysentery occur in Australia and are somewhat common in Queensland and New South Wales.

In the South Pacific amebiasis and amebic dysentery are prevalent in New Guinea, the Solomon Islands, New Caledonia, New Hebrides, the Gilbert and Ellice Islands, Fiji, New Ireland and New Britain. At the date of writing (1944) amebiasis has not proven to be a cause of much sickness among our troops serving in the South Pacific, undoubtedly due to the extreme care taken to prevent infection by proper treatment of water supplies and supervision of food.

Amebic dysentery is prevalent in practically every country embraced in tropical Africa and occurs sporadically throughout that continent. In Egypt this phase of amebiasis is very commonly observed as well as in Morocco, Tunis and Tripoli. It is common in Algeria, British East Africa, the Congo region, Togo, the Ivory Coast, and throughout the countries about the great lakes and those traversed by the rivers of tropical Africa.

As regards the Americas, amebic dysentery is most frequently encoun-

tered in the Argentine Republic, Brazil, Chili, Peru, Venezuela, Colombia, Ecuador, Panama, Honduras, Nicaragua Guatemala, and Mexico. It occurs sporadically throughout tropical America and in the islands of the West Indies, especially in Cuba, Porto Rico, San Domingo and Haiti. In all of these countries amebiasis is very common where sanitary conditions are poor and amebic dysentery occurs in a certain proportion of the cases. In some regions it would appear that continued reinfection has brought about considerable resistance to the parasite as the natives apparently have a very low incidence of amebic dysentery although amebiasis is so widespread among them.

Amebiasis is prevalent in Canada, as shown by Porter (1934) and among 139 patients examined for *Endamoeba histolytica* in the Royal Victoria Hospital, in Montreal, no less than 18 infections with this parasite were demonstrated.

In the United States cases of amebic dysentery have been reported from practically every state in the Union and there can be no doubt that many cases are wrongly diagnosed annually, because of the widespread belief that this type of dysentery occurs only in the tropics or sub-tropics. While this phase of amebiasis is most frequently observed in the Southern States, cases of amebic dysentery have been noted in the most northern tier of states and that it may occur in epidemic form in such localities during the summer months was well demonstrated in the Chicago outbreak of amebic dysentery in 1933. Amebic dysentery is most frequently observed in the United States in Louisiana, Texas, Georgia, Florida, California, Mississippi and Alabama, but a considerable number of cases have been reported from Virginia, Maryland, the District of Columbia, and the Carolinas. In this country attacks of dysentery caused by *Endamoeba histolytica* are very frequently of mild character and for this reason are not suspected as being amebic dysentery, and it is undoubtedly true that a careful examination of the feces of all cases of bloody diarrhoea occurring in all parts of the United States would result in the demonstration that a very considerable portion are of amebic origin.

While amebic dysentery is not very frequently encountered in the United States, as compared with the tropics, it is not infrequently seen in the Southern States and amebiasis, as will be noted in the discussion of the incidence of this infection, is very common in certain parts of this country.

Chapter II

THE ETIOLOGY OF AMEBIASIS AND AMEBIC DYSENTERY

Classification and Nomenclature of the Parasitic Amebae of Man; *Endamoeba histolytica*. Morphology, Habitat, Life History, Cultivation, Experimental Infection of Lower Animals. Relation to Disease.

All of the clinical symptoms which accompany infection with *Endamoeba histolytica* are caused by the invasion of the tissues of man by this parasite and complicating infections with the bacteria that may be present in the intestinal tract. Just what proportion of the symptoms are caused by the ameba and by associated bacteria has never been scientifically ascertained but the evidence is sufficient to prove that *Endamoeba histolytica* is largely responsible for the symptoms peculiar to amebic dysentery although a portion of the clinical picture is undoubtedly caused by complicating bacterial infections, for it is impossible to conceive of severe lesions produced by the amebae being present in the intestinal tissue without associated invasion by bacteria and consequent production of some symptoms of such invasion.

Classification and Nomenclature of Parasitic Amebae of Man

The parasitic amebae of man belong to the Protozoa, single-celled animals, and are placed in the class Rhizopoda. Many species of parasitic amebae occur in the lower animals, as well as in man, and they are all characterized by a body composed of a mass of cytoplasm in which is found a nucleus, or nuclei, ingested material and vacuoles. Several species of parasitic amebae occur in man but only one pathogenic species, *Endamoeba histolytica*.

The classification of these minute animals has always been a very difficult problem owing to their small size, simple morphology, our lack of knowledge of their life-cycle in some respects, the technical difficulties inherent in the study of such minute cells and the differences of opinion voiced by protozoologists regarding the classification of genera and species. At the present time the following classification has been agreed upon by most protozoologists but it may well be that future investigations may render it necessary to change it in some respects.

Genera and Species of Parasitic Amebae of Man

Genus I. Endamoeba Leidy, 1879.

Species in Man: *Endamoeba histolytica* (Schaudinn, 1903), Hickson, 1909.
Endamoeba coli (Grassi, 1879), Hickson, 1909.
Endamoeba gingivalis (Gros, 1849), Smith, Middleton and Barrett, 1914.