THE DIFFERENTIAL PATHOLOGY OF DYSENTERY[1]

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The differentiation of diseases of the gastro-intestinal tract particularly those accompanied by symptoms of diarrhea or dysentery is noted throughout the literature of medicine from the time of Hippocrates to the present (1). One might say that during this period the greatest emphasis was placed on disorders of this tract in the first half of the nineteenth century when Broussais, perhaps the dominant medical figure of that period ascribed all human ills to its disorders or in his own words considered gastro-intestinal disease "the basis of all pathology."

While the first clear descriptions of dysenteric conditions were recorded in 1506 by Benivieni, the differential pathology awaited the arrival of the cellular school headed by Rudolf Virchow who in 1853 described catarrhal and diphtheritic dysentery as stages in one and the same disease. The greatest treatise on the subject of dysentery or of the dysentery group of diseases up to the present time was written by Woodward in the medical history of the Civil War published in 1879. His clinical descriptions together with the notes of autopsies enable one to make presumptive diagnoses of the condition present which in some instances were confirmed in 1925 by the gross and histologic examination of the tissues in the collections of the Army Medical Museum.

The work of Robert Koch and later that of Kartulis 1886–1891 of the Egyptian Cholera Commission did much to establish the characteristics of amebic and bacillary dysentery. Increasing interest in both forms of dysentery about the first of this century stimulated the protozoologists and Schaudinn especially added to our knowledge of the parasitic amebae.

The work of the United States Army physicians in our colonial possessions is responsible for increasing interest and the establish-

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ment of many facts which while in general agreement with the work of the protozoologists required further explanation. The work of Walker and Sellards (1911), cleared up many of the discrepancies between the findings of the protozoologists and the physicians with reference to amebic infection from the standpoints of the etiology and epidemiology of the condition.

The cultivation of parasitic ameba in 1925 by Boeck and Drbohlav led directly to the work of Craig (2) who added other methods of cultivation, demonstrated that extracts of amebae possessed histolytic power for tissue and also caused hemolysis of red blood corpuscles (3). He thus definitely established the etiology of the histolytic changes which we see in human tissues and explained the anemia which appears to be excessive in amebic infection often when other indications of the disease are slight. In addition he added complement fixation to our methods of diagnosing infection by *E. histolytica* (4).

The isolation in 1897 by Shiga of a bacillus in the bacillary form of dysentery followed by the isolation of another type of organism in 1900 by Flexner established a differentiation from the bacteriological standpoint. The finding of the parasites has gradually become to be depended upon for diagnosis to such an extent that differentiation by other methods has been relegated too far in the background much to the detriment of the early diagnosis and treatment of these conditions.

The result of this dependence on exact laboratory diagnosis is nowhere better shown than in the studies of dysentery in Mesopotamia during the World War. In this campaign dysentery was a most serious cause of ineffectiveness among the British troops and was first considered to have been of amebic origin. The work of Ledingham, Penfold and Woodcock, in 1915, together with that of Wenyon and O'Connor, and Dobell resulted in establishing that the majority of these cases were not of amebic origin while the studies of Bahr and especially of Willmore and Shearman, definitely established by a study of the clinical records and the exudate in the stools that most of the cases were of bacterial origin. All this work while in no way decreasing the value of the accurate diagnosis by protozoological and bacteriological study,

shows the danger of depending on these methods alone for the differential diagnosis of dysentery and dysentery-like conditions. It is my purpose to cover differentiation from the standpoint of pathology including therein essential features of the clinical picture, the morbid anatomy and the examination of the stool or rather the exudate contained therein. For this purpose the lesions due to the protozoa, *E. histolytica* and *Balantidium coli*, the dysentery bacilli and the infection accompanying food poisoning by the Salmonella group will be considered.

AMEBIC DYSENTERY

The work of Walker and Sellards indicated that for infection to occur by way of the digestive tract the cyst of *E. histolytica* must be ingested and the work of Hegner, Johnson and Stabler (5) indicates that excystment takes place in the small intestine. Studies in experimental infections by Hegner and his associates and of natural infection by James (6) and others, shows that the ameba makes its way between the epithelial cells and the basement membrane into the depth of the intestinal glands where it dissolves and displaces epithelium. Eventually it invades the submucosa probably along the natural defects of the muscularis mucosae, the atria for blood vessels and lymphatics. There is very little microscopic change in the glandular layers though when the infection is by very numerous organisms there is visible lysis of the tissue and various types of superficial erosion and ulceration not unlike those seen in the lower bowel of experimental animals infected with trophozoites. In both the gland layers and the submucosa the lesions are characterized by the lysis of tissue and the absence of reactive or inflammatory phenomena.

The experimental work of Ratcliffe (1931) (7) suggested that the usual portal of entry is the solitary lymphatic nodule but the early lesions described by James and the work of Hegner indicate the probability that infection occurs in other locations than through the stoma-like crypts in the mucosa overlying the solitary nodules. While it is possible that the destruction of the mucosa over a considerable area may precede and be the method of formation of the amebic ulcer, the more probable stages in the

formation consist in the progression of the amebae to the submucosa along vessels and lymphatics and the formation of small areas of cytolysis (amebic abscesses), their discharge on to the surface, their involvement in secondary infection by the bacteria of the intestinal lumen and the gradual extension of the ulcer partially as a result of a secondary infection but particularly as a result of the peripheral lytic action of the ameba. If the secondary infection is of a mild nature symptoms may be almost entirely lacking. If, on the other hand, a member of the dysentery group invloves the ulceration, severe symptoms, namely those of bacillary dysentery will occur while a streptococcus may lead to the phlegmonous type of reaction so common in inflammations of the appendix. Destruction of a vessel wall by the ameba may lead to a frank hemorrhage and thus for the first time call attention to the pathological process in the intestine. The principle point needing emphasis is that the amebic lesion is one showing characteristic changes of the activity due to the parasite, cytolysis, and practically no reaction on the part of the tissues until secondary infection occurs when the reactive phenomena are due to that secondary infection and not to the parasite. It has recently been my fortune to observe the lower intestinal tract through the sigmoidoscope in cases of amebic ulceration in periods when no clinical symptoms of dysentery were present. The characteristic picture which is more or less familiar to you is that of shallow depressions with overhanging edges and slightly dull bases sometimes a little reddened sometimes paler and slightly opaque. The overhanging margin is usually paler than the normal pink of the surrounding mucosa but may show some spots of injection while in a colon in which there are many of these areas an occasional one may show considerable inflammatory response. This inflammatory response I would interpret as being the picture which would spread over the entire affected area in case of infection with more virulent organisms, the condition usually met with when symptoms become evident. This non inflammatory type of lesion is occasionally seen at autopsy on persons with amebic ulceration of the colon who have died from some other cause, the amebiasis being without obvious symptoms

at the time. This picture is in sharp contrast to the intense reactions of bacillary dysentery. Here let me emphasize the value of the sigmoidoscope in the diagnosis of amebic infections of the lower colon and rectum and also for determining the effect of specific treatment on amebic lesions. The gradual closing of the ulcers leaving minute pale areas at the sites of the former lesions in relatively short periods of time is well worth observing and definitely shows the effectiveness of the specific treatment.

The exudate as seen in the stool in amebic dysentery is consistent with the pathology just described. The erosion of the mucosa even without obvious secondary infection will give rise to desquamation of degenerated tissue cells and the escape of red blood corpuscles and a certain number of leukocytes in addition to the amebae. The tissue cells, leukocytes and red corpuscles show changes consistent with the action of the ameba, namely, a solution of the cytoplasm of the tissue cells and leukocytes so that 60 to 90 per cent of the nucleated elements in the exudate consist of nuclei with little or no cytoplasm surrounding them, the so called pyknotic bodies. This finding alone is sufficient for a presumptive diagnosis of amebic infection and I have yet to see such an exudate without eventually finding *E. histolytica*. The red corpuscles when few in number stain poorly and tend to form clumps (Anderson's phenomenon), while occasionally Charcot-Leyden crystals are present. This pathology is in keeping with the clinical picture which, except for hemorrhage, consists of occasional periods of abdominal distress with or without obvious dysenteric symptoms. The dysenteric symptoms depend upon secondary infection and therefore may vary over a wide range. When they are of an acute nature attention should be directed towards them. Mild catharsis, a bland diet and rest should be used so that these may be alleviated prior to the initiation of specific treatment. This is certainly true if emetin is to be used. My experience with the arsenical preparations is not sufficient to enable me to judge of the safety of using them during acute, febrile attacks.

It is interesting to note how *E. histolytica* maintains the character of its lesion in other organs where secondary infection some-

times plays no apparent rôle. In the liver at autopsy occasionally one finds an amebic abscess without obvious secondary infection and the amebae themselves are rare in the "pus," appearing to reside in the relatively unchanged wall of the lesion. It was recently my fortune to study the exudate from an amebic abscess of the liver which had been draining for months through a sinus between the ribs. A definite stoma having a very minute opening had formed and even this stoma was closed by a flap-like valve of granulation-like tissue. The sinus discharged irregularly a few cubic centimeters of thin mucus-like material streaked with blood. Smear showed the characteristic amebic exudate without bacteria and cultures, aerobic and anaerobic, were negative. The sinus was enlarged and two days later the gauze was removed and was teeming with *E. histolytica* about one-third of which were actively motile. Culture from the gauze from the depths of the wound were again sterile but the outer few centimeters of the sinus showed staphylococci in culture. Recently a case of amebic abscess of the liver of twelve (12) years duration, with amebic empyema of 1000 cc. of typical amebic exudate, gave a similar picture.

E. histolytica appears to free itself of bacteria in passing through the tissue, for reactive phenomenon do not occur in the lesions until after these have opened onto the surface and bacteria have gained entrance. The discharge of the amebae from such a lesion may cause secondary lesions to occur in a similar manner and by this method an increase in the number of foci may occur. The extent and rapidity of the progress of the infection depends first on the number of organisms which succeed in making their way into the tissues and second, on the numerical increase of the organisms in these primary lesions. Large numbers of organisms occasionally appear to invade considerable areas of mucosa and progress directly down and even through the muscular coats of the intestine much as a body of troops infiltrate a wooded terrain. I have seen several such invasions, one of which appeared to be that of a primary infection for no other type of lesion was present. It was characterized by hemorrhagic areas composed of frayed tissue elements with no surrounding inflammation and section

showed enormous numbers of amebae infiltrating through the submucosa and entering the muscular coat yet there was practically no cellular reaction in the vicinity.

In the intervals between dysenteric exacerbations in intestinal infections with *E. histolytica* masses of exudate in the crevices of formed stools indicate the presence of ulceration. The typical picture in such exudates is that of trophozoites in small numbers, precystic forms and cysts with a scanty cellular exudate which still retains the characteristics seen during the exacerbations. Concentration methods may be required to find the cysts of the parasite and it is in such cases that the complement fixation test is of special value.

BALANTIDIAL DYSENTERY

It so happens that *Balantidium coli* was first observed in cases of clinical dysentery (Malmsten, 1857) though an organism indistinguishable from it is a common parasite in the intestinal tract of the domestic pig. Therefore, though of recent years Balantidial Dysentery has been more frequently observed in the tropics it was first seen in the North Temperate Zone. The parasite is a large, free swimming ciliate having both rotary and forward movements. Its cilia are larger than most bacteria. It enters the tissue in a similar manner to *E. histolytica* but because of its size and active movements it produces more damage to the tissues and appears to carry bacteria with it. The superficial lesions consist of loss of substance of parts of glands especially at the base of the crypts in the solitary lymph nodules though ingress to the tissues is not confined to these atria. In searching for early lesions blocks must be made from essentially normal appearing mucosa in which occasionally one will find balantidia forcing their way beneath the epithelial layer to the base of the gland while in other sections they will be found beneath the muscularis mucosae often in masses of leukocytes, a considerable portion of which are of the polymorphonuclear variety. In such abscesses the balantidia often appear degenerated but usually at some distance from these abscesses are groups of apparently normal organisms embedded in rather dense

fibrous tissue which is relatively avascular. The lateral spread of the parasites is accompanied by a surrounding fibrosis which may be partly due to a tissue reaction to foreign substances or to scars of healing infection or both. At any rate the succeeding change is one of death or necrosis of the mucous membrane over the indurated areas, the sloughing of the mucosa and the formation of an ulcer which becomes secondarily infected with intestinal bacteria.

There is considerable evidence also that this parasite may be found in the discharges of the intestinal tract of man without any lesions in the intestine: in other words a condition duplicating the usual one found in the pig. When lesions occur abdominal distress quite like the early symptoms of amebic dysentery occurs and the parasite is easily found in the stool In the early stages few leukocytes are present in the exudate and these show only those changes resulting from their stay in the bowel. The peripheral cytoplasm is not digested as in amebic dysentery and one might term them ordinary or normal leukocytes in contrast to the definitely changing cells seen in amebic dysentery. There is no evidence of lytic action by balantidia in the lesions of the intestine and it is believed that the leukocytic response is due to secondary infection. As secondary infection takes place in the ulceration the leukocytic exudate increases but unless dysentery bacteria gain access to the lesions the character of the leukocytes does not change.

No other protozoal organisms have so far been proven to produce pathological lesions in the intestinal tract of man.

BACILLARY DYSENTERY

Bacillary dysentery is an acute infectious disease characterized by a rapid onset with more or less severe intestinal symptoms, fever, leukocytosis, dehydration and prostration. Except in the milder attacks it does not resemble protozoal dysentery from a clinical standpoint. Severe secondary infections of amebic ulceration may give rise to the symptom complex of bacillary dysentery as the secondary invading organism may be of the dysentery group. When this occurs the acute infection should be

treated without paying attention to the protozoal infection until the acute symptoms have subsided. The pathological anatomy is characterized in the least severe cases by swelling and minute ulcerations in the solitary lymph nodules with more or less intense inflammation of the intervening tissue. In the more severe infections while the lymph nodules may be involved primarily the intense inflammatory reaction spreads over the entire bowel and rapidly progresses from edema to diphtheritic types of inflammation and finally to extensive ulceration with sloughing of the mucosa. Microscopically there is a rapid infiltration of leukocytes of the polymorphonuclear variety though considerable numbers of lymphocytes are also present. This infiltration together with edema dominate the cellular picture. Included among the cells are more or less numerous large mononuclear cells many of which have ingested red corpuscles and leukocytes. Necrosis of the diphtheritic exudate and the upper layer of the mucosa occurs quickly. The leukocytic exudate and inflammatory edema is most marked in the submucosa causing extreme thickening of the intestinal wall.

The exudate in the stool corresponds and consists of 90 per cent leukocytes, the nuclei of which show toxic degeneration but no cytolysis. Macrophages are more or less numerous and are still being erroneously diagnosed as *E. histolytica*. Blood is usually present in greater or lesser amounts but shows no change of diagnostic importance. The continuation of the toxic action of the organisms on leukocytes and macrophages leads to the destruction of the nucleus of these cells leaving peculiar ghost-like forms consisting of the periplast and a few chromatin particles, the so called "ghost cells."

Bacillary dyentery requires prompt treatment if deep ulceration and subsequent scarring of serious nature is to be prevented. One is not justified in waiting for bacteriological diagnosis. Serum treatment given in the first six to eight hours will avoid deep ulceration and the clinical picture and the characteristic exudate make possible a presumptive diagnosis which is correct at least as often as culture. If a few sporadic cases of food infection are treated no harm will result. Use specific treatment

early, keep the intestine free from harsh foods and prevent the formation of scybala until there is no longer evidence of exudate in the stool without reference to the results of terminal culture.

Post-dysenteric ulceration is the usual sequel of bacillary dysentery treated too late after the onset or treated improperly. The lesions consist of indolent ulcers with the thickened fibrous wall of the intestine forming the base over which the mucosa is attempting to grow. Scybalous fecal masses rub off the newly formed margins of these ulcers and this epithelium and a greater or lesser number of leukocytes more or less degenerated from their stay in the bowel may be found in the crevices of formed stools. Following such irritation there may be a recurrence of dysenteric symptoms, and the exudate may be like that of the late stages of the primary process though usually macrophages are few or absent. The exudate does not have the characteristic of that seen in any stage of intestinal amebic infection. It may, however, be confused with ulceration due to other causes such as ulcerated cancer and possibly in some countries where Schistosomiasis of the intestinal type is present it might be confused with the exudate seen in that condition though the eggs of the Schistosomum serve to differentiate. When abscesses open into the intestine the exudate is usually frank pus and is not very confusing. Allergic reactions to food are characterized by a large proportion of eosinophiles in the exudate and there may be an occasional macrophage. In this condition the clinical history should assist in the differentiation.

Poisoning by mercury gives rise to an exudate which is frankly purulent; the leukocytes do not show the toxic degeneration of bacillary dysentery and are often unusually well preserved. Here again the clinical data usually serve to assist in differentiation.

FOOD POISONING

When living organisms are ingested in food infected by bacteria of the Salmonella group there occasionally occurs a colitis which cannot be differentiated clinically or by the stool exudate from the milder cases of bacillary dysentery. When the material

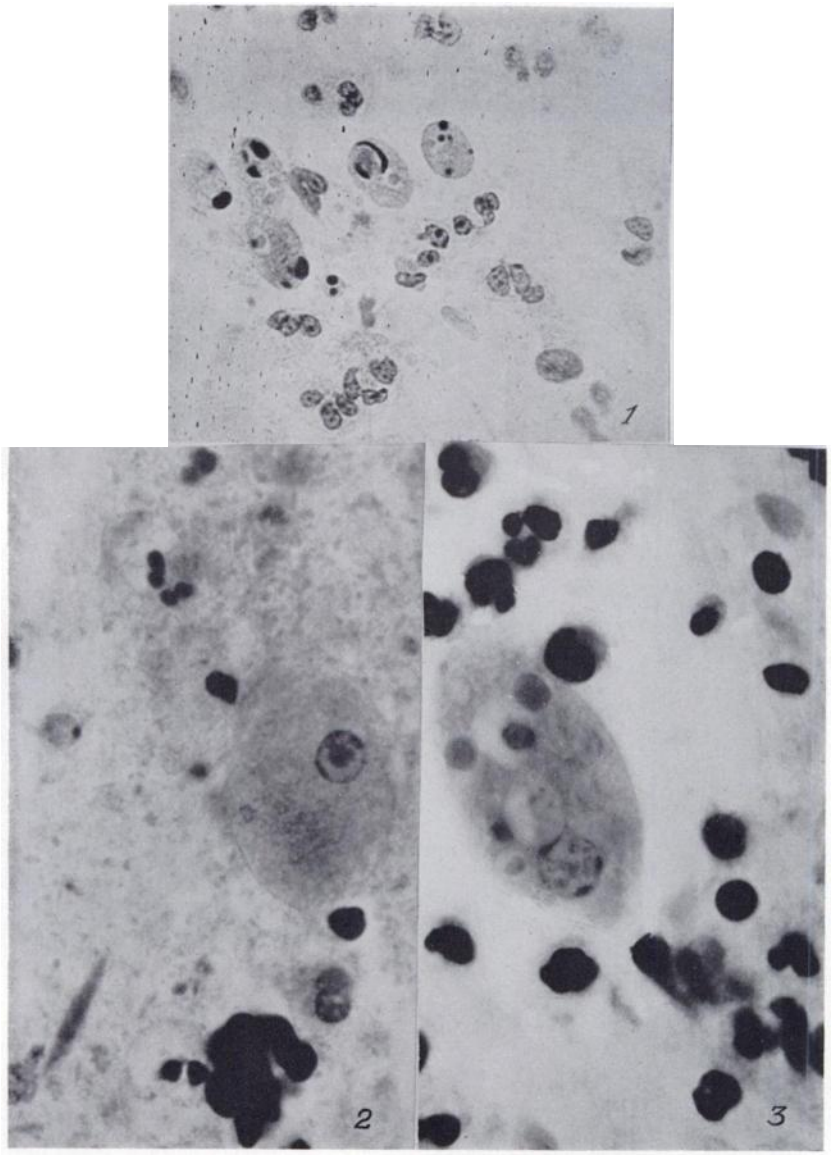

FIG. 1. EXUDATE OF BACILLARY DYSENTERY THREE HOURS AFTER ONSET

Four macrophages at left center. The one farthest right is a "ghost" cell. The leukocytes show "ringing" of the nuclei, an evidence of toxic degeneration.

FIG. 2. SMEAR OF EXUDATE IN AMOEBIC DYSENTERY

Amoeba does not contain corpuscles. Charcot-leyden crystal slightly out of focus, lower left corner. To the right of this a leukocyte showing lysis of cytoplasm. Directly to the right, a clump of red blood corpuscles. (Anderson's phenomenon.) Just below the amoeba and to the left of its upper extremity are pyknotic bodies. The background is composed of bacteria.

FIG. 3. EXUDATE FROM LIVER ABSCESS DUE TO E. HISTOLYTICA

Leukocytes show pyknosis and lysis of cytoplasm. The elements to the right of the amoeba are mostly pyknotic bodies resulting from this lytic degenerative change. Background is free of bacteria.

not only contains living bacteria but also a considerable quantity of the poisonous products produced by them the clinical symptoms may be extremely severe and in young children or debilitated adults may lead to fatal results. In the fatal cases in children

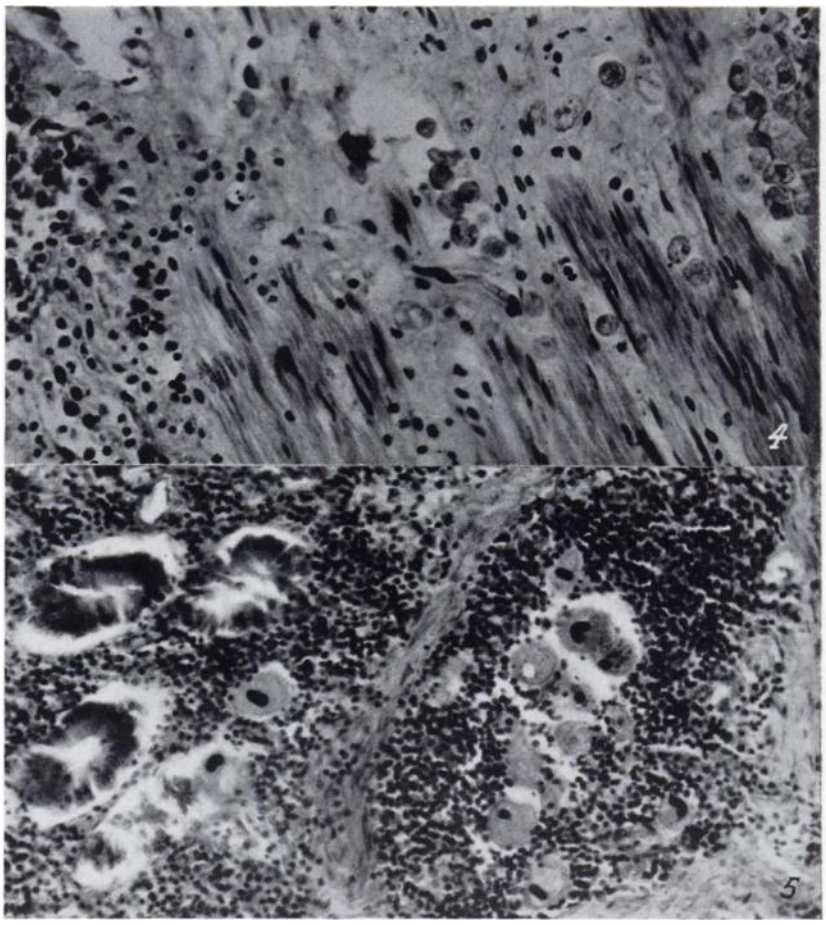

FIG. 4. INVASION OF MUSCLE OF INTESTINE BY E. HISTOLYTICA AND LYSIS OF THE MUSCLE WITH DEGENERATION AND FORMATION OF PYKNOTIC BODIES
Submucosa shown in left lower corner

FIG. 5. INVASION OF INTESTINE BY B. COLI
Two balantidia in the mucosa and a group of partly degenerated ones in a small abscess beneath the muscularis mucosae.

spreading ulceration apparently originating in the solitary lymph nodules appears as the characteristic lesion. In food poisoning epidemics accompanied by this infection the exudate is similar to that seen in bacillary dysentery due to organisms of the Shiga and Flexner group. It is in fact a dysentery. The general treatment, however, is the same and the use of specific serum in such patients will do no harm. The criteria for differentiation are really epidemiological. Food poisoning involves practically all members of the group eating the poisoned food. In bacillary dysentery while the epidemic may be explosive the incidence curve usually shows a relatively gradual rise. The two conditions should not be confused unless one confines himself to the examination of the stool and ignores all other features concerned. As in bacillary dysentery treatment must be continued until the ulcerations have healed.

In conclusion may I state that such opinions as have been expressed were formed after considerable study of the conditions discussed beginning over ten years ago. These opinions have been strengthened rather than weakened by succeeding study and experience. It seems to me that before we accept pathogenicity for a parasitic organism it must be associated with definite pathological lesions even though for lack of susceptible animals Koch's laws cannot be fulfilled in their entirety.

Also with respect to the bacterial agents especially it seems to me that one must expect clinical dysentery or acute colitis, if you prefer, to be caused by other than the bacillus of Shiga and those of the Flexner group just as we find organisms other than the pneumococcus producing inflammation of the lungs or pneumonia. Each organism however will be associated with major or minor variations in the morbid anatomy of the lesions and to some extent in the clinical symptoms and epidemiological characteristics of the diseases produced. In other words, we are past the era where the finding of a disease producing organism in a diseased individual proves the etiological relationship of that organism to the disease.

SUMMARY

1. The pathology of lesions of dysentery is determined by the parasite, protozoon or bacterium causing it.

2. The pathology of infection with *Endamoeba histolytica* is characterized by lysis of tissue cells, leucocytes and red blood corpuscles with little or no inflammatory reaction until and unless secondary bacterial infection of the lesions occurs.

3. The pathology of infection with *Balantidium coli* is characterized by traumatic injury to the intestinal mucosa and secondary infection of the traumatized areas by bacteria carried in by the parasite.

4. The pathology of infection by bacteria of the dysentery and food poisoning group is acute inflammation, the intensity of which varies over a wide range.

5. The differentiation of the kinds of dysentery requires a consideration of the characteristic action of the etiologic agent which is mirrored by the epidemiology, clinical picture, cytology of the exudate, and confirmed by the pathological anatomy.

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