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Etiology of ulcerative colitis

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ULCERATIVE COLITIS

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PREFACE

The conflict over the etiology of ulcerative colitis has maintained a prominent position in medical thinking and medical literature during the last half century. Hence, it is with considerable misgiving and a sense of inadequacy that the preparation of this paper is undertaken. One is naturally afraid to add to an already too voluminous literature on the subject. So much has been written, and so much work has been done, that, at first thought, one jumps at the conclusion that this, at least, is one field for the novice to shun. On the contrary, here is a problem one may approach with full confidence that it will offer many a challenge to ingenuity and reason. Though the solution of the problem may not be found, one gains much, in a broader sense, by reviewing and utilizing the experience of those who have dealt with it before.

In the past, much of the confusion has resulted from lack of adequate definition of terms. Consider the hypothetical case of bacillary dysentery which is acquired during an epidemic. The diagnosis is established by isolation of the organism from the dysenteric stool, and the agglutination reaction of the patients serum confirms the diagnosis. The case is followed for a year through recurrent episodes of diarrhea and constipation, until finally an ulcerated friable, bleeding mucosa is observed. Now the organisms are absent,

the agglutination is negative. Should the disease now be called "chronic bacillary dysentery" or "ulcerative colitis"? Many such cases are on record. The problem is a real one. The same type of question might well be applied to many of the theories of the etiology of the disease.

The difficulties of isolating either Endameba histolytica or the organisms of the Shigella group has certainly added to this confusion. One may safely assume that the diagnosis of these diseases has frequently depended upon the laboratory report of these organisms, just as the diagnosis of chronic ulcerative colitis has depended upon the negative laboratory report, even though the practitioner is quite aware of the limitations of the diagnostic procedure.

It is to be hoped that the presentation of the material in this paper will not serve to add more confusion to an already confused topic, but rather serve to organize and clarify the topic. A real service can be one by merely collecting, under one cover, much of the conflicting evidence.

With the report of some recent investigation in this matter, an effort is made to point out some trends of recent research--as well as to indicate other avenues of investigation that may ultimately yield more information concerning the etiology of ulcerative colitis.

HISTORICAL BACKGROUND

Although the symptoms of diarrhea and the entity of tropical dysentery has been known for many centuries, it was not until 1859 that any definite account of the syndrome of ulcerative colitis appeared in the medical literature. It was only natural that the disease was included in accounts of dysentery appearing before this time. Wilks, (1) in the first description of the disease in 1859, was well aware of its confusion with dysentery. In the publication of his lectures given in the summer of that year we find the following statements under the heading of "Ulcerative Colitis". "If all forms of inflammation of the colon, or colitis, are to be ranked as dysentery, then the results of the inflammation must also be included under the same term, and all ulcerations of this part will receive the name dysenteric--that is, in fact adopted by some; if, however, it be so, we can only say that between simple ulceration and acute dysentery is a wide difference, only to be explained by the view that the latter is a disease of tropical climates, and the former, the less severe and more chronic affection occuring in our own country. We are much in want here, as elsewhere of a more precise definition of terms." As we shall see later, this is a remarkably accurate evaluation of the problem to be uttered almost one hundred years ago.

In 1888 White (2) published a report of 29 cases which at autopsy were found to have had ulceration in the colon. He classified three of these as ulcerative colitis and the others, he thought, were due to secondary effects of other systemic diseases. He clearly recognized the difference between ulcerative colitis and the acute form of tropical dysentery and tuberculous enteritis.

Further light was thrown on the subject, when in 1875 Lösch (3) published his description of ameba occuring in the dysenteric stool. However Endameba histolytica was not established as a pathologic entity until 1891 by Councilman and Lafleur. (4)

In 1898 Gemmel (5) reported an epidemic of ulcerative colitis in an asylum in England. There were 118 deaths in the institution. It is now evident that this epidemic was most certainly bacillary dysentery, rather than ulcerative colitis.

In 1898 Shiga (6) published his report of the bacterial agent causing an epidemic of dysentery in Japan. This report was soon followed in 1900 by the report of Kruse (7) working in Germany and Flexner (8) working in the Philippine Islands.

In 1902 Vedder and Duval (9) working under the direction

of Flexner were able to prove that several epidemics of dysentery occuring in this country were of bacterial origin.

THE BACILLARY DYSENTERY THEORY

Flexner, in 1906 (10) recognized the occurence of an indefinite group of intestinal inflammations, not belonging to either the amebic or bacillary groups. While he does not suggest that the dysentery organisms are the cause of ulcerative colitis, he does offer experimental evidence that ulceration of the mucosa of the colon often results from systemic poisoning, and may be related to the secretory function of the colon.

Since the discovery of the specific etiological agents that cause bacillary dysentery, the view has been held by many that the dysentery organism may be the cause of ulcerative colitis, or that ulcerative colitis may be the terminal stage of chronic bacillary dysentery.

Hurst, in 1921, (11) was impressed by the similarity of ulcerative colitis and bacillary dysentery. In 1931, (12) he again published another paper in which he attempts to rectify certain discrepencies in the knowlege concerning the two diseases. He, of course, knew that the disease known as tropical dysentery in England at that time was apt to occur in epidemics, but that ulcerative colitis was peculiar in its sporadic distribution. In this regard he says; "It is easy to understand how adults occasionally become infected with ulcerative colitis, due to B. dysenteriae, from children with these conditions, and yet do not themselves start a house

epidemic, just as all of the cases of amebic dysentery seen in England have been isolated ones. It is well known that it is difficult to isolate B. dysenteriae from stools of patients in the tropics suffering from typical dysentery, after the acute phase has passed. —— Achlorhydria, which is generally secondary to gastritis was present in 25% of my cases. This is an important predisposing cause, as the absence of the normal acid antiseptic barrier of the stomach allows organisms to reach the intestines."

The view that the dysentery organisms are the cause of ulcerative colitis was also held in Canada by Thorlakson. (13) His opinions are the result of clinical impressions and no experimental evidence is offered.

In 1936 Felsen (14) reported 42 consecutive cases, which had been previously diagnosed as ulcerative colitis, in which a diagnostic agglutination titre against B. dysenteriae was obtained. He further cites 7 cases of acute dysentery which were followed over a period of a year who subsequently developed symptoms similar to ulcerative colitis during this time. His more recent studies seem to support this point of view. (15) His experience with bacillary dysentery and ulcerative colitis in World War II is particularly interesting. (16) (17) He concludes that his study of chronic ulcerative colitis in 61 military

personnel and others working in military areas reveals an intimate association with outbreaks of acute bacillary dysentery. Positive cultures were present in 41.6 per cent of those studied during the acute phase and in 9.8 per cent after the development of chronic ulcerative colitis. He believes that this again indicates the general truth of the aphorism that "the ideal treatment of chronic ulcerative colitis is the prevention of bacillary dysentery."

The experience and observations of D'antoni, which were reported in 1943, (18) further demonstrates an interesting relationship between bacillary dysentery and ulcerative colitis. He says, in part, "Since 1935 more than 150 cases of the disease which I have termed Shigella colitis have been observed. This exceeds the number of cases of bacillary dysentery observed from the same sources over the same period, though it is probable that the geographic distribution and epidemiology of the two diseases are much the same. Not more than 20 or 30 per cent of the cases with Shigella colitis give a history of previous dysentery".

He was well aware that there are significant psychological changes associated with the disease. His description of the typical psychic reaction pattern follows: "The patient, who was formerly in perfect health, finds that over a period of years he has become high strung,

nervous, irritable and easily fatigued. Ambition is lacking, and if he is in a responsible position, he may ultimately find it is necessary to resign from it, with resulting change in his financial and business status. Abdominal symptoms are usually in the form of sharp, shooting, variously located pains. As a rule, the patient has consulted many physicians and his condition had frequently been diagnosed as neurosis of undetermined etiology. From 70 to 90 per cent of the patients with Shigella colitis whom I have observed present this syndome, the mechanism of which is still to be elucidated!

D'antoni further points out the difficulties in making the diagnosis from laboratory studies. He reports that the diagnosis could rarely be made from the first examination, and that in some cases 20 examinations were required. In the 150 cases reported above, he found that on the average 5 examinations had been required before a positive diagnosis could be extablished.

In another paper, published in the same year, D'antoni (19) reviews 236 cases in which the presenting complaint was diarrhea. The incidence of various etiological factors is quite interesting. Endameba histolytica was recovered in 68 cases. Shigella organisms were cultured from 21 cases. In addition Lymphopathia venerium was responsible for 3 cases,

undulant fever was found in 7 cases, carcinoma was found in 5 cases, intestinal tuberculosis was found in 3 cases, stronglyloidiosis was responsible for 3 cases, hook worm was found in 2 cases and Giardia were found in one case. He felt that pellegra was a contributing factor in several other cases.

Reid, Anderson, Stubblefiels and Ivy, in 1934, (20) studied the effect of intravenous administration of Shiga toxin in a large number of dogs. Petechial hemorrhages in the stomach, hemorrhagic pseudo-membraneous enteritis, and hemorrhages into and ulceration of the colon were found.

In 1939 Lium (21) reported that he was able to produce ulceration of exteriorized patches of the dog intestine by injecting non-fatal doses of Shiga toxin.

It is interesting to note that there is evidently a specific affinity for the intestinal mucosa by the Shiga toxin, and this is of course amply confirmed by the clinical course of the disease. One might conclude that since this be true, the mucosa of the colon could also possibly be susceptible to some other type of toxin.

The fact that the dysentery organisms cannot be isolated from cases of ulcerative colitis holds less significance when the preceding clinical experiences and the following experimental evidence is considered.

In 1933, Paulson(22) reported that in undiluted and diluted non-coaguable human blood, taken from both normal and bacillary dysentery cases, Bacillus dysenteriae (Shiga and Flexner) failed to survive, when incubated at 37°C. In bullion controls they grew abundantly. The experiments suggested that the presence of fresh blood in the intestine, might explain, in a measure, the inability to isolate these organism from patients with chronic bacillary dysentery or ulcerative colitis, as the case may be. It would further indicate that in consequence of this negative bacteriologic study, many cases of bacillary dysentery may have been classified as ulcerative colitis.

The agglutination reaction may not be reliable in these cases for Mackie in 1939 (23) was able to demonstrate that the agglutination reaction was practically worthless in the diagnosis of Shigella colitis. It is well established that the reliability of the agglutination reaction decreases with the increase of time elapsing between the onset of the attack and the performing of the agglutination test. It may be added that many cases finally diagnosed as chronic ulcerative colitis are studied intensively for the first time years after the initial attack.

OTHER BACTERIAL THEORIES

Early studies on the bacteriology of ulcerative colitis yielded a variety of conflicting results. Bacillus coli, the proteus group, the pyocyaneus group and various streptococci were isolated from the colon of patients suffering from ulcerative colitis by Jex-Blake in 1909. (24) He considered them to be the cause of the disease.

Wallis, in 1909, (25) found streptococci in the stools of patients suffering from ulcerative colitis and emphasized the significance of oral sepsis in ulcerative colitis.

In 1911 White (26) isolated bacillus coli and pneumococci from the stools of patients with ulcerative colitis and considered them both to be of etiological significance.

In 1911 Bassler (27) published results obtained by culturing the rectal mucosa of 4 patients having ulcerative colitis. These cultures demonstrated that Bacillus coli communis was present in all cases and that the organism resulted in fatal infection when injected into the peritoneal cavity of rabbits and Guinea pigs and cats. In a later paper (28) he suggests that the organism could become virulent under the proper conditions and suggested that the organism be called "Pseudo-dysentericus coli". He also states that pseudomonas and proteus vulgarus and streptococcus fecalis could be cultured from these cases and

that they may play a role as secondary invaders.

Yoeman's conclusions were opposed to the above for in 1921 he stated that he could culture only the usual intestinal organisms from the stools of these patients. (29)

Hewes, in 1923, (30) isolated streptococci, colon bacilli and the gas bacillus from cases of ulcerative colitis. He believed that there was some factor, as yet undescribed, which would account for the "idiopathic invasion of the colon in persons of perfect health".

In 1941, Weiss, Slanger and Goodfriend (31) offered the opinion that the disease was due to a mixed infection. They cultured the noses and throats of 15 cases of ulcerative colitis and found Staphylococcus albus 6 times, non-hemolytic Streptococci 4 times, Streptococcus viridans twice, hemolytic Staphylococci onee, and Micorcoccus catarrhalis once. In the cultures from the recto-sigmoid of these patients they found Bacillus coli 9 times, and Staphylococcus albus 5 times, non-hemolytic Streptococci were found 3 times, hemolytic Bacillus coli twice, and one strain of hemolytic Streptococci was found. They prepared the so-called combined vaccine from these cultures. Fourteen of the patients received this combined vaccine and all recovered. One patient who received only the vaccine prepared from the recto-sigmoid showed no

improvement, but when the cultures from the nose and throat were included in the vaccine, the patient recovered.

In contrast to this Winkelstein and Schwartzman, in 1942, (32) reported that they used a concentrated, purified, antitoxic Bacillus coli serum. They report excellent results in 51 per cent of the cases so treated, good results in 17 per cent of the cases, questionable results in 7 per cent of the cases and failure in 25 per cent of the cases.

Swartz and Jankelson described the fungi they had isolated from 24 cases of ulcerative colitis in 1941 (33) They were able to isolate fungi of the Geotrichum group in 66.6 per cent of the cases and Monilia in 12.5 per cent of the cases. Both types of organisms were isolated from 8.3 per cent of the cases. From their control group of normal individuals they were able to isolate these fungi only 33.3 per cent of the time, while in the cases of ulcerative colitis, they were isolated 87.5 per cent of the time. They observed that all those cases which harbored Monilia were quite severe, and in two instances the disease rapidly terminated in death.

In contrast to the above findings, these two types of fungi have been repeatedly isolated from the skin and colon of normal individuals. Hopkins and his associates, in 1933 (34)

reported that they had found organisms of the Geotrichum group on the skin of normal individuals 41 per cent of the time, and Monilia albicans 18 per cent of the time. Schnoor, in 1939, (35) in a series of 314 normal subjects found Monilia albicans present in the stool 16.1 per cent of the time and Geotricum was present in the stool 29 per cent of the time.

In 1942, Henderson, Pinkerton, and Moore reported a case of ulcerative colitis which they believed was caused by Histoplasma capsulatum. (36)

From these investigations it appears that it is not probable that any of the above fungi are regularly the responsible infecting agent in ulcerative colitis.

THE DIPLOCOCCUS OF BARGEN

In 1924, Bargen, (37) working at the Mayo clinic, was attempting to isolate a dysentery like organism from cases of ulcerative colitis. He noticed, however, that in the direct smears from the ulcers a gram positive diplococcus was very frequently present. When swabs, taken from the rectal mucosa of these patients were cultured in deep brain broth by the method described by Rosenow in 1919, (38) frequently he found that a gram positive diplococcus was the predominating organism. He believed that the gradient of oxygen tension found in these deep tubes was the determining factor that enabled him to successfully isolate the organism. In this study 28 patients were included and cultures from 15 of these, when injected intravenously into rabbits, produced lesions in the colon of the rabbits. The diplococcus could subsequently be recovered from the colitis produced in the rabbit. However 190 rabbits were injected with cultures from the 15 patients and only 56 developed lesions in the colon. His control group includes only four patients and indeed one of them harbored organisms which produced petechial hemorrhages in the rabbits colon when injected intravenously. Hence, he was able to produce lesions of the colon in rabbits 29 per cent of the time from a group of patients selected from a larger group of 28. In his inadequate control group

injections of the cultures from 4 patients without colon pathology produced lesions in the rabbit colon 25 per cent of the time. However, he was quite convinced that the diplococcus was the cause of ulcerative colitis. In this first paper Bargen suggested the use of a vaccine, to immunize against this organism, prepared from cultures made from the colon of each individual case. He reported its use in 5 cases, 4 of these left the clinic in an improved condition.

Continuing his work along this line, Bargen reported again in 1925 (39) that in a group of 68 patients he was able to isolate the diplococcus from 80 per cent of them. 139 rabbits had been injected with 5 to 15 cc quantities of brain broth cultures from these patients. In 45 of the rabbits so injected, there were demonstrable lesions in the colon but no lesion appeared elsewhere. In attempting to determine the factors which caused the diplococcus to localize in the colon, he kept 18 rabbits on a vitamin deficient diet consisting of crushed oats and water or autoclaved rice and water for a period of 2 weeks. At the end of this time 8 of them were injected with 5 cc of the brain broth culture of the diplococcus. All of the rabbits died within 5 days and 8 of them had lesions of the colon and in addition, 3 of the 8 had developed an empyema of the gall bladder from

which the diplococcus could be isolated. Of the 8 control rabbits on the vitamin deficient diet, 5 died with signs of starvation and vitamin deficiency, though 4 of them lived for 2 months. The diplococcus which had been re-isolated from the gall bladders of the rabbits was then injected intravenously into 2 dogs in daily amounts up to 20 cc. By the fourth day both dogs had developed a bloody diarrhea and pathological changes in the colon which he thought was typical of ulcerative colitis. It is interesting to note, however, that in spite of repeated daily injection of 20 cc of the brain broth culture, both dogs improved, and after the acute phase, both recovered. He concluded that focal infection of the gall bladder could be related to ulcerative colitis in the human.

He reports experimental work on two interesting cases, one of these a woman, 26 years old, entered the clinic and a diagnosis of ulcerative colitis was made. Vaccine treatment was started but resulted in a more severe diarrhea and soreness in a tooth which had previously been devitalized. X-ray of the tooth revealed an apical abscess. It was removed and subsequently infected tonsils were removed. These procedures resulted in a very severe exacerbation of the colitis. Cultures from the apical abscess revealed a diplococcus,

similar to the one previously described, which was quite pathogenic for rabbits. The young woman was treated by vaccine filtrate and in two weeks was entirely well. In this paper Bargen also describes his method for preparing the vaccine and the vaccine filtrate, but advises that the usual treatment be used also. He further reports 12 cases clinically well and nine case much improved from the use of the vaccine or the filtrate. He reports no failures from the use of the vaccine or the filtrate.

In 1930 Bargen (40) reports a group of 23 cases who had quite atypical varieties of ulcerative colitis, in that there was a regional or segmental distribution of the involved areas of the colon. The diplococcus which he previously described was cultured from 11 of the cases and cultures were not taken from 10 of the cases. All were treated with his vaccine. 15 were cured, three were greatly improved and 5 succumbed to the disease or its complication. He postulates that the peculiar anatomical distribution of the disease in these cases may indicate that the disease is blood born, or it may indicate that the disease may start in the rectum, progressing orad and healing behind as it progresses. He does not say why such a distribution of of the lesions would cause one to think that it would be a blood born disease.

In 1933 Bargen and Buie (41) reported further experimental and pathological evidence that they thought implicated the diplococcus that they had previously isolated. They state that 815 strains of the organism had been isolated from 1,100 patients and 500 of these strains had been injected into rabbits. They report that lesions in the rabbit colon which resembled ulcerative colitis in man resulted in 65 per cent of the instances. They also report that the organism had been isolated from the blood stream of 8 patients acutely ill with ulcerative colitis. They further state that the organism had been found in periapical dental abscesses in 148 cases of ulcerative colitis and in the latter group they could produce the characteristic pathological change in the rabbit colon 75 per cent of the time by injection of the cultures taken from these periapical abscesses. They further state that the organism had been found in infected tonsils in 100 cases of ulcerative colitis, and that injection of cultures from these gave identical results with those obtained by injection of cultures taken from the periapical abscesses. In this same paper they describe the pathologic changes in the colon and state that the primary lesion is a small submucosal abscess which results from the occlusion of the capillaries by infected emboli.

Bargen in his discussion of the verification of his work refers to Rosenow's theories of focal infection and elective localization. (42) This, of course brings a host of theories and data before us that are beyond the scope of this paper. However, Rosenow was able to demonstrate such elective localization in rabbits 58 per cent of the time in 527 instances. However, he used a control group of 1,329 and in this control group, the intestinal tract was involved only 5.2 percent of the time. Unfortunately he does not give the source of the organism which were used in the control group.

In 1938 Bargen and his associates (43) reported a statistical analysis of 1,573 cases of ulcerative colitis which they had seen at the Mayo clinic. 500 of these were finally diagnosed as amebiasis and 73 proved to be of tuberculous origin. Of the remaining 1,000 cases Bargen believed that 871 presented typical clinical, proctoscopic and radiological evidence of being of bacterial origin. The remaining 129 were atypical. They were particularly interested in the 871 cases which they believed to be caused by the diplococcus. The histories of these cases were studied to determine what the immediate, predipitating factor was in the development of the disease. They found that in 108 cases the onset of the disease was associated with an upper respiratory

infection. A few other factors were mentioned, but in 571 cases no immediate, precipitating factor could be determined. They further found that in these 871 cases, 134 had relapses which were associated with upper respiratory infections, but in 650 cases no other factor could be determined. The cases were also analyzed from the standpoint of age, sex, clinical progression and complications. They could conclude that the disease is more severe in children and decreases in severity as age increases. However, no other significant findings were presented to indicate the etiology of the disease.

Cook, in 1931 (44) performed a series of experiments, the results of which support the experimental results of Bargen and his associates. He cultivated a diplococcus from the abscessed teeth of patients with ulcerative colitis. 60 rabbits were injected intravenously with the usual broth culture and 60 per cent of them developed hemorrhagic lesions of the colon and 21 per cent of the rabbits developed lesions elsewhere. He subsequently innoculated the teeth of 15 dogs with the diplococcus which had been isolated from the teeth of patients who had ulcerative colitis. Seven of the dogs developed diarrhea and ulcers of the colon, which were detected and followed proctoscopically from 8 to 16 months. 60 rabbits were again injected with the broth culture of the

teeth of the dogs at the end of the experiment; this time 40 per cent developed lesions of the colon and 21 per cent developed lesions elsewhere. Cooks experiment was well controlled for he used cultures from devitalized teeth from patients with diseases other than ulcerative colitis. He followed the same procedure through. Injections into 60 rabbits produced lesions in the colon in one. When he inoculated the teeth of 15 control dogs with these cultures, none of them developed colitis.

While the clinical results obtained as benefit from the results of laboratory experiments must remain the final test of the value of those experiments, in this case they are especially hard to evaluate. First, it is known that ulcerative colitis is a disease that is characterized by exacerbations and remissions, and second, very few of the reports of clinical success carry any report of the exact diagnostic methods that have been used. In view of the difficulty of isolating intestinal bacteria and parasites, and the altered immunological reactions that are known to occur, one must be very hesitant about drawing conclusions from clinical results in ulcerative colitis.

These difficulties, not withstanding, Bargen and Buie (45) published the results of their treatment of 1472 cases at the Mayo Clinic from 1923 to 1933. They report that

ileostomy was required 78 times and that there were 40 post-operative deaths from the procedure. 54 of the patients died from "other causes" and the remainder were benefited or cured by the use of the so called Bargen vaccine.

In 1933, Paulson, (46) in his evaluation of Bargen's work was very critical of the fact that the only criteria used in the identification of the organism was its morphology. He states that organisms presenting these characteristics have been isolated from normal human feces by a technique which has been previously described. He offers the following facts as evidence opposing Bargen's theories. First, the presence of blood, favoring the growth of cocci normally present, may result in their becoming pathogenic and continuing the process. Todd (47) has also demonstrated that the passage of streptococci through serum alone, in many instances will re-establish virulence. It was thought, also, that other organisms, normally present in the intestine, surviving in this abnormal medium, may assist, to a lesser degree, in carrying on the involvement. If the production of colonic lesions in animals by intestinal bacteria is of import, then further support for this belief is to be had in the fact that more profound lesions are caused by mixed, rather than pure cultures.

Paulson further states that if the streptococci were in predominance (thus having an etiological role in the disease) one would find an absolute increase of the cultures on blood agar plates, while such is not the case. He believes the use of a selective medium for the isolation of the organisms lessens the significance of the fact. Such can hardly be the case, for it is generally known that many types of highly virulent organisms require selective media for their isolation and subsequent identification.

In his later papers, Bargen recognized the role played by allergy and in one paper specifically states that cases of allergic colitis were excluded from the tabulations. (48)(49)

It is interesting to note that he also recognized the psychic factors in the disease for in 1933 he wrote; "rebuilding morale is one of the most important steps in starting the patient on his way to recovery". (50)

BACILLUS NECROPHORUM OF DACK AND DRAGSTEDT

In 1934 Dack (51) became interested in the experimental pathogenesis of bacillary dysentery and was experimenting with the infection of a Thiry-Vella fistula that he had established in two adult rhesus monkeys. He noted a change in the bacterial flora after the fistula was formed. This led him to investigate the changes in the bacterial flora of the human colon after an ileostomy had been done. The cases selected for the subsequent study were three cases who had required ileostomy for ulcerative colitis. (52) They had observed that in some patients ileostomy does not cause the colon to heal and that it may discharge blood and pus for years following the operation. Cultures were taken from the colons of these patients and they discovered that over a period of months there was a definite tendency for the aerobic organisms to disappear and that they were replaced by anaerobic ones. The predominating organism was an anaerobic, fusiform fod, which, at times, would form long filamentous growths. They state that though this organism had not been previously described, it closely resembled the Bacteroides of Thompson and Beaver (53) and the Actinomyces necrophorus of Shaw (54) and Cunningham (55) and the Bacillus necrophorus of Orcutt (56).

The organism was shown to be pathogenic for rabbits

and using an antigen prepared from it, they were able to demonstrate compliment fixing antibodies by the Kolmer method in the sera of 4 patients suffering from ulcerative colitis. They also found that the sera of 5 patients with ulcerative colitis contained agglutinins specific for this organism. Control agglutinations from 3 healthy individuals were negative, while the fourth contained a trace of the agglutinin.

Continuing their work with this organism, they were able to isolate the organism from 14 patients who were ill with ulcerative colitis. (57) They also found that they could demonstrate compliment fixing antibodies in these same 14 cases. In a series of 16 normal individuals they found that there were weak concentrations of the compliment fixing antibodies present in 3 instances.

In a later paper, published in 1937, the cultural and antigenic characteristics of the organism were reported (58). It was found that it was pathogenic for rabbits and that specific agglutinins could be produced. However, testing the effect of the antisera by injecting it into rabbits, along with known virulent strains of the organism gave indecisive results. The organism was not pathogenic and did not grow when introduced into the colon of a rhesus monkey. However, they did find that repeated curettage of the normal colon mucosa in two sphinx baboons was followed by

ulceration and that subsequently Bacterium necrophorum could be isolated from these ulcers.

In an effort to clear up the exact identity of the organism that they had isolated from cases of ulcerative colitis, Dack and his co-workers, in 1938, (59) compared the cultural and pathogenic aspects of the organism with other organisms they had isolated from liver abscesses in cattle. This was the source from which a similar organism had been isolated in other reports. They concluded from these studies that the previously reported Bacterium funduliforme could not be differentiated from their organism which they had designated as Bacterium necrophorum.

By 1939 Dack and his co-workers (60) had accumulated 6 strains of Bacterium necrophorum that would not agglutinate spontaneously and they considered these to be suitable for further study of the immunological characteristics of the organism. These 6, further more, presented different antigenic structure when tested with immune rabbit serum. They reported agglutination reactions found in the sera of 36 cases of ulcerative colitis. They grouped the results according to the severity of the disease.

CONCENTRATION OF AGGLUTININS
FOR B. NECROPHORUM CORRELATED TO THE
SEVERITY OF THE DISEASE

Dack, Kirsner, Dragstedt, Johnson 1939 (60)

Severity of Disease	No. of Patients	Positive Cultures	Agglutination of B. Necrophorum (over 1-40)
0 (mild)	5	1	1
1	11	2	4
2	18	7	8
3	18	9	13
4 (most severe)	13	11	9

They also report that agglutinins may also rarely appear in the sera of individuals suffering from other diseases of the colon and rectum and the titre in these instances closely parallels the extent of the disease.

They conclude that "Bacterium necrophorum appears to be constantly present in the diseased colon of chronic colitis. The basis for the extension of the lesions in this disease, as contrasted with localization in other types of ulceration of the colon where Bacterium necrophorum is present in large numbers, is a matter of prime importance in considering the etiology of ulcerative colitis. It is quite apparent that some factor or factors peculiar to patients with chronic ulcertive colitis render the tissues vulnerable to a spreading infection with Bacterium necrophorum predominating".

It is of interest to note that in this connection it has repeatedly been shown that the colon of the normal monkey is quite resistant to infection with the dysentery bacilli, but when the animals are kept on a vitamin deficient diet, the Flexner type of dysentery bacilli appear frequently. (61)(62) Thus, at least in monkeys, a vitamin deficiency is similar to the factor postulated above.

Dack and Walker reported the antigenic relationships of 12 strains of the organism in 1939. (63) They found

considerable variation in the antigenic structure of the various strains, but this could not be related to the virulence of the organism as demonstrated in laboratory animals.

In 1939 Dack and his associates reported results obtained when the colons of 99 normal individuals were cultured. (64) In no case did they isolate Bacterium necrophorum but the organism could be cultured in 27 instances out of a series of 38 cases of ulcerative colitis.

Recognizing the role of cutaneous sensitivity in many other chronic infectious diseases, Dack and his associates, in the following year, concluded that an evaluation of the role of Bacterium necrophorum could not be complete without some consideration of this aspect of the problem. (65) Accordingly 12 patients with ulcerative colitis were tested for cutaneous sensitivity to organisms that had been isolated from their colons. This test was performed by intradermal injections of suspensions of the killed organisms. Injections of the same antigens were given to 15 healthy persons as controls. Both groups reacted to the antigens, and the reactions in both groups were similar. They concluded that this reaction was inflammatory in nature and not related to any specific sensitization resulting from the disease.

In summarizing their research on Bacillus necrophorum as a cause of ulcerative colitis, Dack and Dragstedt reported

in 1941 (66) that in a period of 8 years they were able to isolate the organism from 70 per cent of 298 cases, and that most of the failures were encountered during a remission of the disease. They reported that cultures taken from 99 normal individuals did not demonstrate the organism. They point out that similar organisms are pathogenic for domestic animals. While ulcerative colitis has not been produced in laboratory animals by this organism, subcutaneous abscesses are readily produced in rabbits. They stress the point that the organism is known to be pathogenic for man in other locations, but that it has little invasive power. They conclude that the organism is probably a secondary invader, and that some other factor is probably required to initiate the process.

It is interesting to note what T. R. Brown(67) wrote in 1925 concerning this concept. "Is it not possible that the cause of the disease is to be found not in the presence of a definite and specific infective agent, but rather in the absence of some protective factor or substance or mechanism, or of something which normally inhibits the bacterial invasion of the intestinal wall, perhaps due to a metabolic error or endocrine disturbance or lack of a specific bacteriophage, or absence of some normal bactericidal substance in the intestinal mucosa?"

ALLERGY

The role played by allergy in the pathogenesis of ulcerative colitis has received more attention in recent years, though its exact relationship to the disease is still poorly defined.

Andreson, in 1925, (68) recognized that gastrointestinal sensitivity could occur, and that it need not be associated with cutaneous sensitivity to the offending antigen. However, he did not observe any relationship between allergy and ulcerative colitis.

In 1934, Kramer (69) offered the opinion that allergy could be a factor in a variety of gastro-intestinal conditions, but again he did not ascribe a definite etiological relationship of allergy to ulcerative colitis.

Hare, in 1935, (70) studied the life histories of 38 cases of ulcerative colitis. In this group he found that 85 per cent of the cases had a personal or family history of some disease of allergic origin. This was of special significance to him because of Bruce Pearson's data which demonstrated that a personal or family history of allergic disease occured in 26 percent of normal individuals. (71)

In 1938, Gray and Walzer(72) demonstrated that the rectal mucosa in the human could be passively sensitized. They were fortunate enough to have a patient who demonstrated

a high degree of clinical sensitivity to peanut protein. 0.05 cc of the serum of this patient was injected into the rectal mucosa of 38 normal individuals. This was followed in 1 or 2 days by a meal consisting largely of raw ground peanuts. Every member of this group demonstrated a marked allergic reaction at the sensitized site, a few minutes after the injestion of the peanut meal. This reaction could also be elicited by rectal instillation and topical application of the peanut protein.

They subsequently found that the mucosa of the colon, ileum and the peritoneum of the rhesus monkey could also be sensitized in the same manner. (73)

This work deomonstrates that the mucosa of the ileum, colon and rectum is capable of an allergic reaction, though passive transfer of sensitivity to this area does not prove that it could, actively, develop a local tissue sensitivity similar to the Schwartzman phenomena. (74) However, it is of great clinical significance to note that at least some types of antigens are absorbed, unaltered in their immunological reactions, almost immediately after introduction into the gastro-intestinal tract.

In 1940, Rubin (75) described 4 cases of intestinal bleeding in the new born. All of these infants were under 8 weeks of age and all were on a cows milk formula. Three of

the four subsequently developed severe infantile eczema, in spite of the fact that all recovered from the gastro-intestinal complaint when cows milk was eliminated from their diet.

In 1942 Rowe (76) described his results in 14 cases of ulcerative colitis, using the elimination diet which he previously described. (77) He found that 7 of the 14 cases completely recovered under his care. He considered wheat, eggs, milk and fish to be the most frequently encountered antigens in these cases.

In 1942 Andreson (78) also found food allergy to be responsible for ulcerative colitis in certain instances. He was able to demonstrate food allergy in 66 per cent of a series of 50 cases. He found that this gastro-intestinal sensitivity occured in the absence of cutaneous sensitivity.

PSYCHOSOMATIC ASPECTS OF ULCERATIVE COLITIS

In 1930 Murray (79) published the first description of the psychogenic factors in the etiology of ulcerative colitis. 12 cases were studied and detailed records of 4 of these are reported. All of these patients demonstrated deep-seated emotional conflicts. In the 5 women studied in this series the emotional conflict revolved around marital problems of some sort. None of the 7 males were married and for the most part, the emotional problem was a conflict between a mother fixation and a desire for marriage. However, it is of considerable significance that in two of the cases Endameba histolytica were found in the stools and both of these cases improved on specific therapy.

In 1935 Sullivan (80) reported a series of 28 cases of ulcerative colitis. 18 of these were studied from a psychiatric standpoint and in 15 of the cases emotional disturbances appeared to be of definite etiological significance. He suggests that "emotion through the diencephalon whips the liquid contents of the small intestine down into the colon. In these particular individuals, the enzymes in this liquid intestinal content may be of a higher digestive power than the normal or the natural protective powers of the colon may be lowered. At any rate surface digestion of the colon occurs and bacterial invasion is made easy and acute

ulceration results. Because of the fact that the emotional difficulty remains a chronic one, the hypermotility of the intestinal contents persists, and the constant irritation results in a chronic colitis. When the emotional conflict is solved, the intestinal motility returns to normal and the chief irritative factor is removed and the colon can now take care of its bacterial invaders."

Wittkower, in 1938, (81) studied the personalities of a series of 40 cases of ulcerative colitis. In 37 of the cases to studied, the colitis was antedated by psychological abnormalities or definite psychological disorders well beyond the range of normal. No uniform personality type was discovered, though obsessions, and hysterical reactions were common. The cases studied were divided into groups according to the personality reaction type. Group I consisted of 17 patients whose personality was characterized by over-conscientiousness, Over-scrupulousness, orderliness, cleanliness and obstinacy made up the obsessions. Group II contained 12 patients whose personality was characterized by emotional lability, temper tantrums, childishness, self-centeredness and suggestibility. Hysterical reactions were found most commonly in this group. Group III consisted of 6 cases with schizoid personalities or depressive tendencies. Wittkower observed that these patients frequently suffered exacerbations of the disease following

an emotional disturbance which would have been considered minor in the normal personality. He concludes that while the aberrent psychological background may not be the whole cause of the disease, it does play a distinct etiological role.

More recent studies have continued to confirm that there are significant psychosomatic aspects of the disease. In 1942 Daniels (82) reported a series of 25 cases, and the results of psychoanalysis of 14 of these. There were 2 men and 12 women in the group. He reported that 8 demonstrated pathologic attachment to a relative and in six of these the death of the relative had assumed paramount importance. Two demonstrated marked indecision about marriage. In two others engagement and marriage precipitated the first attack. In two more the first symptoms appeared immediately following child birth. Four demonstrated excessive worry over money matters.

In a later paper, published in 1944 (83), Daniels further describes the type of personality that is apt to be involved in ulcerative colitis. He reports the following. The personality is self-centered and narcissistic and dependent. There is frequent dependence on the mother or this may be transfered to an older sister or other in-laws. There is emotional and sexual immaturity. Males are seldom

married, females are more often married, but tend to be fussy housewives. Psychiatric disorders are much more frequent than in the general population. Mental depression is frequent in the course of the disease. Suicidal drives occur, and hysterical conversion is common. There is often found some precipitating factor such as emotional disturbance or conflict. Symptoms may occur within 48 hours of such disturbance. Pregnancy appears to be more of an emotional strain than a physiological one. In men attachment for the mother may conflict with sex drive and desire to marry. Death or sickness of a near relative, expecially if the patient is attached to that person, is important.

In 1946, West (84) reported favorable results in two out of three cases of ulcerative colitis, using psychotherapy in the treatment of the disease. The third case which he so treated passed on into a deep psychosis.

MISCELLANEOUS THEORIES OF THE ETIOLOGY OF ULCERATIVE COLITIS

The thought that ulcerative colitis may be a specific deficiency syndrome has occurred to many workers. At present there is little convincing experimental evidence to confirm this point of view. There are, however, several highly suggestive reports to be found in the literature. Gill's report in 1944 (85) of the use of feedings of raw pig intestine is especially interesting in this regard. He reasoned that if this were a deficiency disease the missing factor might be supplied by the pig intestine. He used six cases in his series. Four of the six obtained definite benefit. One of the cases has remained well over a period of ten years by taking about one half pound of pig intestine a day. On four occasions in the ten years he stopped eating the pig intestine, and each time suffered a relapse, and again improved upon returning to the diet containing the pig intestine.

There have been a limited number of studies on the possibility of some altered physiologic or metabolic process contributing to the disease. However, most of the conclusions seem to be that any physiological difference that is demonstrated is probably the result of the disease and not its cause. In 1943, Bercowitz and Page (86) found that the glucose tolerance curve is apt to be high and prolonged when the glucose is given orally, but that these curves are normal when the glucose is given intravenously. It appears that

there is a delay in the absorption of glucose associated with the disease. The basal metabolic rate, and the respiratory quotients of all the patients studied were within the normal range.

They also found that a large percentage of the cases had definitely elevated prothrombin times, but concluded that this was probably the result of the disease, and had no relationship to its cause.(87)

Another portion of these studies were concerned with the absorption of vitamin A in patients with ulcerative colitis. (88) They compared the result obtained in a group of 25 cases with ulcerative colitis and eight normal adults. Their method was the use of an oral dose of 100,000 units of Vitamin A in fish liver oil, and then determining the plasma level of vitamin A four hours afterward. The normal cases demonstrated a 46.2 per cent higher rise in plasma vitamin A than did the cases of ulcerative colitis.

Wozasek, Steigman, and Fantus, as well as others,(89)(90)(91) studied the effect of various substances upon the colon. In general, the method was to determine weight, number and moisture content of the stools before and after feeding certain substances. The stools were examined for protein, mucous and cellular elements. Bran, Karaya gum, magnesium

sulfate, fruit, phenolphthalein, cascara and prostigmine were all investigated by this method. The results in each case were quite inconclusive, and the constituents of the stool seemed to be more often an individual characteristic, than to be dependant on any of the above.

In 1941 Poppe (92) reported that he was able to produce colitis in dogs by injecting the mesenteric lymphatic vessels with a sclerosing solution. He concluded that this might be a factor in the pathogenesis of ulcerative colitis in the human. On the contrary, Sinaiko and Necheles (93) reported in 1946 that they were not able to confirm these results.

Steiner and his associates reported in 1944 (94) that they had demonstrated a toxic factor in the livers of cases of ulcerative colitis which had come to autopsy. They were able to determine that the substance was not histamine, though when an extract of the liver was injected into laboratory animals, they reacted in a manner simulating the effects of histamine.

Since the Psychosomatic school had postulated that the increased peristaltic activity that could arise from emotional disturbance might carry the intestinal ferments rapidly into the colon before they were neutralized in the small intestine, it could be reasoned that they could give

rise to digestion of the mucosa of the colon. In 1944 (95) Portis, Block and Necheles reported their findings after analysis of the stools of patients with ulcerative colitis, and analysis of the discharge from ileostomies in other types of patients. They found that the rectal discharge from patients with ulcerative colits did contain a moderate amount of trypsin, though the discharge from ileostomies of patients with ulcerative colitis contained large amounts of trypsin, but not as much as that from patients in whom ileostomy had been done for carcinoma of the colon. It seemed that the length of time the ileostomy had been present was more significant in determining the amount of trypsin present, than was the disease process involved. They also found that perfusion of the colon of the dog with a solution of trypsin leads to irritation, friability and inflammation of the mucosa and hemorrhage and the production of large amounts of mucous.

In 1945, Ivy and Clarke (96) reported an operation that they had performed on six dogs. In these animals the jejunum was anastomosed to the appendix, so that bile and pancreatic juice flowed directly into the colon. The dogs lived from 6 to 23 weeks following the operation. In no animal did they find hyperemia of the mucosa or hemorrhage into the colon. However all animals developed a stomal jejunal ulcer.

SUMMARY

It has been generally accepted that chronic bacillary dysentery may occur as a clinical entity. The technical difficulties in isolating the organism from all cases of bacillary dysentery are also widely recognized, and the unreliability of the agglutination reaction, long after the onset of the disease, is known. In view of these facts, it is felt that most writers neglect to mention the exact procedures which were used to exclude bacillary dysentery, and do not attach sufficient importance to the history of any acute episode which could be interpreted as the acute phase of bacillary dysentery. It is felt that the fact that ulcerative colitis has frequently been encountered where bacillary dysentery is not endemic may indicate that the two are distinct and separate, even though easily confused diseases.

The problem, then, is composed of two factors. The first of these is the differential diagnosis of ulcerative colitis and chronic bacillary dysentery. The second is to decide if the final result of the pathological process, initiated by the dysentery organisms is to be called "ulcerative colitis". D'antoni's comment, made in 1944 (97) is significant, and it is logical to agree with his

practice of using the term "Shigella colitis" to designate this process. He says; "The incidence of the disease obviously depends on the diagnostic ability of the profession; the poorer the diagnosis from the stand point of etiology, the higher will be the incidence of ulcerative colitis."

The confusion of amebic dysentery with ulcerative colitis is well known, and here again there is a distinct need for all who work in this field to be quite specific in reporting the measures used in excluding this disease. It is not uncommon for the case, which has been considered to be ulcerative colitis, to recover under specific anti-amebic therapy. Closer attention to these details in the diagnosis of ulcerative colitis would serve to clarify its status.

Bargens's theory as to the cause of ulcerative colitis has received acceptance by many workers. However, many more have reserved judgement until more accurate data are at hand. Bargen's chief support to his theory is his own results in the treatment of the disease.

It is significant to note again that ulcerative colitis is a disease characterized by remissions and exacerbations. This fact would render such data, derived from response to therapy, unreliable. Satisfactory conclusions could not be drawn unless there were adequate control groups. Unfortunately

Bargen and his associates have taken the attitude that it is unjustifiable to use any other treatment than the one they prescribe, in spite of the fact that other workers have also reported excellent results, using other therapeutic measures.

Those who are interested in the psychiatric aspects of the disease might well point out that the removal from the environment which gave rise to the disease is an important psycho-therapeutic measure. Bargen stresses the importance of morale building, hence psychotherapy, in his own writings. Could not some measure of his success be from the psychiatric readjustment of the patient?

From the allergist's point of view, the use of diets is most important, and of course Bargen, and most other conscientious physicians use a diet in the treatment of ulcerative colitis. However, one may justifiably raise the question as to how much good has been done by the diet and how much by the vaccine.

Dack and his associates are much more reserved in their claim of the role played by Bacillus necrophorum in ulcerative colitis. They recognized that it was present in other pathological conditions, and that its role was probably that of a secondary invader. The immunity to the organism that is developed during the course of the disease and the correlation

of the titre of this immunity and the severity of the disease lend strong support to this claim. They recognize the presence of some other factor which initiates the process. One cannot but conclude that the laboratory work in this piece of research has been accurate and their rational approach to the problem has been an admirable one.

The relationship of allergy to ulcerative colitis is quite indistinct. There is no doubt that gastro-intestinal allergy per se does exist, hence it seems reasonable to assume that the mucosa of the colon can develop active immunity. Gray and Walzer demonstrated that the mucosa has the ability to react to passive immunity, and that unaltered protein can be absorbed from the gastro-intestinal tract, to stimulate the sensitized mucosa to an allergic reaction. The high incidence of family and personal history of allergy found in ulcerative colitis by Hare is quite significant.

The field of psychiatry has now included ulcerative colitis in its realm, and there is, without doubt, considerable justification for this. However, if it be true that the personality of the patient with ulcerative colitis is unstable and suggestible, should not the histories and data obtained from these patients receive careful scrutiny and verification? If such be the case, the personality and opinions of the examiner would most certainly be injected into the final

results of any research work. Those who are not impressed by the significance of the psychopathic personality in the etiology of ulceritive colitis may argue that the personality traits may be a manifestation of the disease and the histories given by the patients, would, most certainly, be effected by the current disability.

No report of the personality traits of these patients, before they developed the disease, has been found. The type of personality described could be expected to be searching for an explanation for the disease. Would it not grasp at any pseudo-scientific explanation, and influence the conclusion from the interviews? One may also find the statement that the abnormal personality is the one that has been psycho-analyzed. Foster Kennedy concluded that "psychiatric aspects of ulcerative colitis may rise from long standing, unrelieved symptoms or from actual cerebral or nervous tissue allergy". (98)

CONCLUSION

Recognizing the role played by secondary bacterial invasion of the colon, and the relationship of ulcerative colitis to allergy, and to the psychopathic personality, and its confusion with bacillary and amebic dysentery, one must conclude that there are many factors which may initiate the disease process. As it is used today, the term "ulcerative colitis" probably indicates the end result of the actions of a variety of etiological factors.

It is to be hoped that future workers in the field will make use of the well-known and reliable custom of controlled experiement, and will base their conclusions on facts proven or already known.

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