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Chronic ulcerative colitis : etiology and diagnosis

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CHRONIC ULCERATIVE COLITIS
ETIOLOGY
AND
DIAGNOSIS

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INTRODUCTION

For years chronic ulcerative colitis has been the stumbling block of many good gastro-enterologists and today this block is stained red with the blood of their conflicting endeavors. Since its first description by Hale White in 1888, the etiology of this disease has run the gauntlet of possibilities and then run back again. Practically every writer who has had either clinical or laboratory experience, or both, with this disease has contributed something different to the knowledge of it. Consequently the literature abounds with myriads of ideas, sound and unsound, about all phases of the disease.

A study of chronic ulcerative colitis has been conspicuously absent from our medical curriculum. Much stress and numerous hours have been given to the subject of typhoid fever, a disease seen much less frequently by the physician of today than the condition dealt with in this paper. A most recent edition of a standard textbook of general medicine fails to give ulcerative colitis more than casual mention. The reason for this is obviously the lack of any unified knowledge, by the profession, of the etiology of the disease and of any particular treatment that adapts itself to it. Adequate

information about ulcerative colitis can be found only in the periodical literature and there it abounds in profusion.

The state of ulcerative colitis was brought home to me during my Junior year while studying a particularly severe case, that of Wm. Tilse, who will be mentioned later in this paper.

The purpose of this paper is to present, without bias (a characteristic notably lacking in the majority of works on this disease) the features of the present tenable theories on the etiology of chronic ulcerative colitis, with an attempt to correlate them and present them, in a compact picture, to the reader.

It seems remarkable that after fifty years of intensive work, the present concept of the disease is tending to swing back to the ideas put forth in the early years of this century.

It is the hope of the writer that this paper will, in some measure, help unify the present concept of the disease and will lead to a more rational and thorough study of the patient.

J.L.B.

DEFINITION

Chronic Ulcerative colitis is an inflammatory disease of the colon of questionable etiology. It is characterized clinically by diarrhea and the passage of blood and mucous with the stool, and pathologically by inflammation and ulceration of the mucosa of the colon and by inflammation and scar tissue formation in the colonic wall which frequently lead to severe and permanent abnormalities of this structure. These changes are accompanied by disturbed function of the colon, and frequently the physiology of the stomach and small intestine is also altered. The disease tends to run a long continued chronic course accompanied by periods of exacerbations and remissions of the condition.

ETIOLOGY

Predisposing factors.

Factors which predispose an individual to chronic ulcerative colitis may be divided into two groups: 1. those associated with the onset of the disease or accompanying the initial symptoms and 2. those which seem to precipitate exacerbations or evidence of recurrence of the colitis.

Larson (29) studied the histories of 233 patients with chronic ulcerative colitis seen at the

Mayo Clinic in the year 1930:

Sex. Sex seemed to have no bearing on the incidence of the disease, 100 of the patients being males and 133 females. Lynch and Felsen (33) noted a similar ratio in their series of cases. They found that married women were affected more than single women.

Age. In Larson's series the age incidence for this disease was about the same as that for any infectious disease--during the most active period of one's life. Of the 233 cases 173 (73%) were between the ages of 20 and 50 years. The youngest patient was twenty-two months of age and the oldest, seventy-three years. Five patients were in the first decade of life, twenty-two in the second, fifty-eight in the third, sixty-nine in the fourth, forty-six in the fifth and twenty-three in the sixth and seventh. Three patients were between seventy and seventy-three years of age, inclusive.

Nationality and geographic distribution seemed to be of no consequence in this disease--the figures corresponding in general with the general population and registration at the clinic. Lynch and Felsen (33) were unable to elicit any evidence pointing to an infection--epidemic or endemic, and almost all of their patients came from localities where good hygienic conditions

existed, and none had traveled to any extent.

Lynch and Felsen, Logan (31) and numerous other writers have repeatedly seen cases in which no other member of the family was affected or gave a history of a similar disease. They concluded that occupation had no relation to the colitis as the great majority of their patients had more or less sedentary occupations not requiring extensive contact with persons or poisonous materials.

In the series of 233 cases studied by Larsen it was found that in 123 (53.2%) a definite predisposing factor was present which seemed to have some relation to the onset of the disease apparently coming on independent of any disturbance of health. In the 124 cases the predisposing cause was definite infection in fifty-two cases; influenza in thirty-one; head colds in eleven; sore throat and appendicitis in two each and otitis media, sinusitis, pertusses, cholecystitis and epidemic jaundice in one each.

Conditions which lower the local resistance of the bowel seem to be a factor of relative importance. In 22.3% of Larson's cases trauma or infection seemed to have afforded a possible mode of entry for the etiological agent. These factors consisted of consti-

pation--treated with laxation and enemas, attacks of diarrhea following ingestion of improperly cooked food or polluted drinking water, amoebic dysentery, epidemic dysentery and local rectal pathology.

Yeomans (53) found similar features in his cases and also believes that dietary indiscretions, exposure, pregnancy, parturition, and surgical operations are significant only as they reduce the natural body resistance. Lynch and Felson suggest that nervous influences at play in nervous shock and hyperthyroidism may possibly exert these effects by means of the excessive peristalsis and diarrhea often associated with those conditions. That psychic factors may have some influence on the disease was found in six of Larsen's patients, and Murray (39) studied the life situation in twelve patients who gave indications that there were deeper problems to be investigated in the psychophysiologic sphere. In all cases there was a well marked time relationship of symptoms. He noted that the outstanding trait in colitis patients besides fearfulness is their emotional immaturity and the inadequate infantile manner in which they face their problems. The relationship of this mental type with the diarrhea is that diarrhea is an infantile response to fear. The organization of the

infant is presumably such that fear is often expressed by excitation of the colon and thus a pattern may be layed down and not outgrown.

Factors which seem to initiate exacerbation of ulcerative colitis follow somewhat the same classification as those which accompany the first symptoms. Here upper respiratory infection plays an even more prominent role. Influenza, removal of foci and sinusitis follow in the order of their importance. (29) In 12 of 20 patients studied for predisposing factors by Bergen and Kembel (8) notable histories of troublesome infections of the nose, throat and teeth were obtained.

Bergen and Rankin (10) reported ulcerative colitis developing postoperatively in 12 cases and leading to fatal results in all cases. Ten of these cases were between 50 and 67 years of age, and gastric surgery was the type performed in half of the cases. The average post operative day for the appearance of the diarrhea was 6 days, the average days survived being 25.8 days with the minimum being 6 days and the maximum 58 days. It would seem that the exciting organism was present in the lumen or wall of the gut at the time of operation, and that postoperatively certain factors were brought into play to cause the etiological agent to become effective.

Bargens and Andrews (47) suggest a parallelism between peptic ulcer and chronic ulcerative colitis but point out that it would seem that worry and psychic disturbances incident to the colitis might be sufficient to precipitate symptoms of peptic ulcer.

SPECIFIC ETIOLOGY

The etiological factors responsible for the disease, chronic ulcerative colitis, have provided the gastroenterologists and bacteriologists with an abundance of material with which to work ever since the condition was first discovered by Sir Samuel Wilks in 1875 and later by White (50) in 1888. Since that time there has been an ever increasing amount of work done in an attempt to demonstrate and prove a definite specific etiological factor. As is expected when a new condition is described numerous theories are rapidly advanced. The extremely severe debilitating and annoying characteristic of the disease, its marked chronicity, its unpredictable occurrence, its obscure nature and its stubbornness in response to the usual type of symptomatic treatment make its study all the more intriguing to the physician. The pitiful picture presented by the patient with profuse, uncontrollable diarrhea with as high as 30 stools passed per day,

headed definitely toward death has made the search for the cause of this disease a mighty one--and justly so. No sadder picture can be imagined.

The search for a specific etiological factor has, until recently, been entirely directed along bacterial lines because of the infective nature of the disease. (53) This view is favored by Einhorn (54) because the great prostration which occasionally appears during the sickness and the septic processes such as arthritis complicating the affection in its late stage. White (50) states that in his cases chronic Brights disease was the commonest complication of ulcerative colitis.

Adequate and thorough examination of the colon and its discharge is rendered doubly difficult because of the extremely large variety and number of organisms present--both dead and alive, and the task of separating the pathogenic from the nonpathogenic organism and their subsequent identification by cultural, morphological and agglutination characteristics represents hours of intricate work. As a result of this work by numerous men several theories of more or less specific nature have been formulated depending upon the various results obtained. In this paper I shall attempt to present the theories most prominent because of their general acceptance or popularity, as the case may be.

Bacillary Dysentery--as an Etiological Factor

The English school has been particularly interested in Ulcerative Colitis from the standpoint of bacillary dysentery and Wilks, who first discovered the disease, pointed out that the condition was anatomically indistinguishable from dysentery (48). White (50) Hawkins (26) and Saundby (45) are of the same opinion. Hurst (28) states that during the World War he was unable to distinguish chronic ulcerative colitis from bacillary dysentery by sigmoidoscopic examination. Paulson (41) performed rectosigmoidoscopy in more than fifty cases of definite acute and subacute and chronic bacillary dysentery in infancy and childhood. No normal rectums or sigmoids were seen and in most instances the appearances were identical with the appearance of chronic ulcerative colitis. Roentgenograms, in both conditions, often were not unlike one another.

In spite of the opinion that the colons of ulcerative colitis and dysentery were identical the difference in the entire clinical picture lead White (50) to state that although the origin of ulcerative colitis was obscure it was definitely not dysentery. In 1904 Flexner (23) isolated Bacillary dysentery from 63.2% of 412 cases of severe diarrhea in New York children

under conditions not presenting epidemic features.

(It was not until 1906--when Saundby (45) and Hawkins (27) in 1909--following occasional isolation of the dysentery bacillus suggested the use of an antidysenteric serum as a specific treatment for the colitis.) Hurst states that in 1913 Nabarro isolated the dysentery bacillus from a child suffering with recurrent colitis for many years and that since that time has repeated this in numerous cases of summer diarrhea as well as cases diagnosed as chronic colitis. In 1931 Wilkenstein (52) isolated dysentery organisms in 4 cases of ulcerative colitis and Mackii (45) in 1934 recorded investigation on 83 conservative cases. Of these 20.4% showed dysenteric organisms in cultures obtained from swabs obtained from the bases of the ulcers, and 42% of the 83 presented cultural or serologic evidence of bacillary dysentery.

Much difficulty is encountered in the scientific demonstration of *Bacillus dysenterae* or proving its presence by serological means. The relation of ulcerative colitis to dysentery can be ideally shown only by adequate scientific measures. Much difficulty has been encountered because of the peculiar cultural and serologic characteristics of the organisms of the dysentery group. Penner (42) points out the diagnostic criteria

necessary to show the relationship of Bacillary dysentery to non-specific ulcerative colitis.

A.

Isolation and Identification.

Culture material is obtained directly from the basis of the ulceration with the use of the proctoscope or sigmoidoscope and the material placed on endplates and the pearly gray colonies isolated to the various sugar media for fermentation reactions as well as to glucose agar slants in preparation for specific agglutination reactions. At this point the variability in the fermentation reaction becomes apparent for both *Bacillus coli* and *Bacillus dysenteriae* may show similar reactions and as such both types of colonies must be subcultured before adequate examination can be made to determine to what group each colony can be ascribed.

Similar variability is likewise found in the dysenteric group itself and as such fermentation reactions cannot be used as the sole measure of identification. In addition, the fermentation reaction will vary in successive tests at considerable intervals and these fermentation differences may show little correlation with antigenic differences. Hence, it may be said that isolation of the bacillus is the only safe method for certain diagnosis of the types of organism causing the infection and that the

cultural characteristics have only a very tentative value. It now becomes necessary to make use of the agglutination characteristics of the suspected organism to establish positive identification, but here again, several sources of error appear which are probably due to variation in the antigenic factors of the bacilli. The organism may show a marked difference in the agglutinability with specific sera from strain to strain, and from time to time in that strain. Thus an organism which culturally and fermentatively appears to belong to the dysentery group may not be agglutinated by specific animal sera. If the organism is definitely one of the dysentery group-- though failure to be agglutinated may be due to: (a) Failure to use the specific serum, (b) Complete or partial temporary inagglutinability. Naturally, the first factor may be remedied by using a larger variety of sera to include the specific type necessary and real inagglutinability is usually not permanent and disappears on repeated subculture. In any case agglutinin absorption methods will usually serve to identify the organism in such instances.

B.

The Significance of the Agglutination Reaction.

This method of demonstrating the presence of dysentery infection is of secondary importance and

provides only presumptive evidence for the following reasons:

1. Positive agglutination may be obtained with the sera of perfectly healthy individuals who give no previous history of dysentery.

2. Healthy sera clump bacilli by virtue of this physico-chemical-constitution and independent of any contact with bacteria in the sense of a previous infection.

3. The intensity of agglutination varies from species to species and from time to time in the same individual and also with the agglutinability of the suspension used.

4. Negative results may be obtained where specific organisms may be repeatedly recovered from the stools (40). Paulson(41) states that Douglas, Colebrook and Morgan, indefinitely established subacute and chronic bacillary dysentery and have shown the serum agglutination reaction to be of no diagnostic importance. Hence the agglutination reaction is of value only when there is definite clinical evidence of bacillary dysentery.

C. Bacteriophagy.

This, likewise, is of little real diagnostic value and is of importance only when more dependable evidence

can be demonstrated; for there is usually a marked cross lysis with the various dysentery strains and also the lytic principle is usually present only during the acute period of the disease as it is beginning to subside so that it is of little value in the chronic case. (42)

D. Incidence and Significance of Chronic Dysentery.

The incidence of chronic bacillary dysentery is of considerable interest and importance as it might show the relationship between it and chronic ulcerative colitis. Taking the arbitrary view that the acute form of dysentery becomes chronic after an interval of three months since the onset--some definite figures can be obtained. As can be seen from the data previously presented, dysentery bacilli have been isolated by numerous individuals in a fairly high present age of cases, thus indicating this importance as foci of dissemination in epidemics and endemics. Froensdorf, in a follow up of 210 cases of acute bacillary dysentery during the war, found only three cases, (1.43%). Albu, on the other hand, basing his opinion on sigmoidoscopic and clinical observations considers complete healing of the intestinal mucosa as rare in bacillary dysentery. Clinically, the colon retains a hypersensitivity, and recurrence of symptoms occur following a slight stimulus. Sigmoid-

oscopic changes persisted for years, but he was only able to demonstrate organisms in 2 cases. Leusden(30) estimated that about 5% of cases of acute bacillary dysentery became chronic. Walko, in discussing chronic bacillary dysentery points out that, in his experience, these cases are practically always infectious, whether merely healthy carriers or chronically ill with persistent or recurrent diarrhea. (42).

E. Epidemiologic Data.

Bacillary dysentery, although generally considered in the realm of tropical disease, is endemic throughout the entire United States practically the year round. Data on the incidence of dysentery in this country, as published in the United States Public Health Reports, show that the disease is reported practically every month throughout the year from coast to coast. This report also shows that cases per 100,000 in childhood for 1931, 1932, and 1933 were 15.7, 12.0, and 12.5, respectively, while for adults for the same years were 2, 1.7, and 2.2. From this it can be seen that endemic dysentery is more prevalent in infants than in adults. This may be contrasted with the relative infrequent occurrence of chronic ulcerative colitis in the infant age period (42).

The role of chronic bacillary as concerned in the clinical picture of chronic ulcerative colitis may be expressed in the words of Penner (42), who summarizes the present day concept, which is like-wise that of Paulson(41):

"The gross clinical features and course of chronic bacillary dysentery and of non-specific ulcerative colitis resemble each other so closely that differentiation is impossible unless we trace a case to a known and proved epidemic--an unusual event. Similarly, the sigmoidoscopic and roentgenologic features are so similar that they cannot serve as reliable methods of differentiation, and finally, we find that even on the autopsy table, there are few if any features which serve as adequate criteria for purposes of differential diagnosis."

"Despite these close resemblances there are other features which make one suggest that the two conditions are not dependant upon a common etiology. Thus, in contrast to the age distribution of bacillary dysentery, as given above, we find a preponderance of cases of non-specific ulcerative colitis in the third and fourth decades with surprisingly few cases in infancy and childhood. Furthermore, despite the wide-spread distribution of epidemic bacillary dysentery throughout the armies on

all fronts during the World War, the preponderance of males is at present below the age of 40, and mainly in the third decade which did not see service over-seas. In addition chronic non-specific ulcerative colitis, insófar as it has been reported in the literature, is not as prevalent in Central Europe as one would expect from the prevalence of acute epidemic bacillary dysentery during the late war.

"Finally, we must contrast the well known lack of infectivity of non-specific ulcerative colitis, for which no authority known to us has ever claimed infective properties, with the equally well known infectivity of cases of chronic bacillary dysentery as pointed out by Walko and Schurer and Wolff. Bergen, in a larger series at the Mayo Clinic, was able to find but five instances of familial occurrence while Paulson, in the Johns Hopkins Hospital series, could uncover only one instance. It has been our experience that where such cases occur we are much more likely to find a definite etiological agent such as amoebae or dysentery bacilli.

"It is our impression that taking the ulcerative colitides as a group these will be found definite etiological agents responsible for a relatively small number and that the larger residual group consists of a heterogeneous conglomeration of conditions with variable etiology."

THE ROLE OF THE STREPTOCOCCUS

The part played by streptococci in ulcerative colitis was presented in 1927 by Bassler (13) of New York City, who ascribed the hemolytic streptococcus as the prominent cause of the disease. Because of the masking of these organisms by the other organisms encountered in direct smear and cultural observation, detection is often extremely difficult, nevertheless, pyogenic, hemolytic, and non-hemolytic streptococci occur in practically all cases of severe ulcerative colitis--in fact in some cases streptococci may be found in almost pure culture.

Paulson (40) made exhaustive studies of fourteen cases of ulcerative colitis in an attempt to isolate bacteria, not including the colon bacilli, from the bases of ulcers and from the mucosa when ulcers were not present, in cases of acute exacerbations of the disease, that he might establish the consistent presence and preponderance of a definite bacterium. By elaborate cultural means, two distinct types of streptococci were isolated in these cases and no one type was present in more than three cases. Eight varieties appeared as alpha-zoned colonies on blood agar and two as beta-zoned colonies. Only thirteen cases showed the presence of

streptococci. In the remaining cases no form other than *Bacillus coli* could be isolated from three swabs, which had been taken from the bases of ulcers on two separate occasions and after the examination of eighteen plates.

The streptococci which were isolated from the cases of acute exacerbation of ulcerative colitis do not have a definite morphology of their own, and any attempt to diagnose any one or more of these organisms on the basis of morphology alone is a futile task. (41) By cultural and fermentation methods, however, the different strains can be identified and there seems to be no tendency for the individual strains to change these characteristics. (42)

In another series of 50 cases (14) Bassler's records show the finding of groups of streptococci in all cases. Hemolytic streptococci were present in forty-two cases, green streptococci in twenty-one cases, and non-hemolytic in seventeen. In but three cases were the green type the only streptococci cultured and in the rest of the cases it occurred with the hemolytic type. Non-hemolytic streptococci were found alone in but two cases. In all the rest the green and the non-hemolytic strains were found with the hemolytic, the green types predominating. Since the hemolytic streptococci are not denizens

of the human intestinal canal, the green and non-hemolytic types being not uncommonly met with, Bassler believes, that it is strongly suggested that the hemolytic types are probably etiological factors of significance in the production of ulcerative colitis.

The production of lesions in the colons of rabbits subsequent to injection of the isolated strains of streptococci was attempted by Paulson (40). Of the ten types of streptococci isolated by morphological, cultural and fermentative means, seven were intravenously injected into thirty-four rabbits, five of which produced lesions in these animals. Thirty rabbits came to autopsy, fourteen of which showed lesions which were primarily in the colon and rectum. Pathological examination demonstrated that these lesions were similar to those of chronic ulcerative colitis. Twelve rabbits developed definite diarrhea with or without blood mucous, clinically in autopsy. Other rabbits were injected intravenously with seven types of bacteria. A heated (killed) culture from a beta-hemolytic streptococcus (foreign protein) isolated from the uterus of one with puerperal sepsis, *Bacillus coli* from a normal human sigmoid and a case of amoebic dysentery and *Bacillus dysenteriae*. Shiga and Flexner produced lesions, confirmed by microscopic section similar in pathology and location to those just referred to.

In advanced cases of the disease, especially the chronic types that have existed for some length of time the simple examination of the feces of two shows an increased dominance of streptococci and a reduction or absence of the more normal organisms. In the lethal cases for quite a while before the end, the hemolytic streptococci, may be the only organism present in the feces (14). In a comparative study of the bacterial flora of normal persons and patients with ulcerative colitis, *Bacillus coli*, *Bacillus welchi* and streptococci preponderate in the latter type (40). Subsequent studies have shown that when fecal emulsions are grown in vitro in human noncoaguable blood in normal and ulcerative colitis cases, by simple technique to stimulate continued bleeding, only streptococci and enterococci survive while in infusion bouillions controls, gram negative bacilli predominate. Under identical condition in diluted blood (1cc of blood to 3cc of saline solution) other organisms live but not as numerously as in boullion, resulting in a quantative diminution of flora and a relative increase, when not absolute, of cocci because of the greater ability of the latter to live in blood than the other intestinal bacteria, which were either destroyed or had their growth inhibited by the bacteriocidal or bacteriostatus

characteristics of the blood. Hence it may be concluded that the diminution of flora observed in chronic ulcerative colitis and a relative increase in the number of cocci is due in part, if not completely to the presence of blood which appears to get, generally speaking, less deleteriously on the cocci than on other organism of the intestinal flora. Thus, the greater and more prolonged the intestinal bleeding, regardless of the cause, the more marked changes of the nature described appear likely to occur (41).

Bassler (14) points out that hemolytic streptococci are not normal inhabitants of the normal gastrointestinal tract but it is quite common for the green and non-hemolytic strains to be present. On the other hand Dukes (22) and Paulson (40) found that there are no distinctive differences, morphologically, between primary dextrose brain broth cultures from material secured from the ulcer bases of cases of ulcerative colitis and those from swabs from cleaned normal colons. In some instances there is an increase in the gram positive organisms in the ulcerative colitis, but such a picture is not characteristic. The normal ratio of gram positive to gram negative organism in the stool is three to seven, and a high protein diet will bring about an increase in the

gram negative organism and a high carbohydrate diet (14) or a diet containing considerable milk will increase the number of gram positive organisms, and smears of broth suspensions of these stools show these cocci to be identical in morphology to stained smears from primary cultures of cases of ulcerative colitis.

This contradictory finding brings up the question that perhaps the hemolytic streptococci may not be the sole etiological factor and that it is possible that other organisms may exist in symbiotic relationship with the streptococcus and as such the role of a mixed infection exists. Careful technical work with feces shows that there are antorganisms between different genus types, and particularly the different symbiotic groupings that are met with. The organisms that in a general way are symbiotic with the streptococci are the *Staphylococcus albus*, gram positive diplococcus (diplococcus of Bagen), certain strains of *Escherichia coli*, *Erythrobacillus prodigiosus*, *Clostridium vedematis maligni*, *Alcaligenes fecaloides*, the *Pseudomonas aeruginosa*, and the *Clostridium welchi*. These symbioses can be proven by culture experiments in mixed inoculations in suitable fluid medias and are definite up to the time that bacteriophagic phenomena occur.

The staphylococcus is demonstrable in stained smears of the feces of approximately 33% of cases of ulcerative colitis and may be found culturally in more than 50% of the cases. While this organism occurs in the stool of non-ulcerated conditions and may at times represent a distinct infection of the intestine it occurs only occasionally. In ulcerative colitis when the hemolytic streptococci are present it is most frequently found. It may exist in the feces in ulcerative colitis for years especially in instances of long recurrences and moderate recurrences. The symbiosing characteristic of the staphylococcus albus (hemolytic) with the hemolytic streptococcus appear quite definite (14).

The role of the gram positive diplococcus, as pointed out by Bassler, is paradoxical for it may be found in the normal intestinal tract, in the stools of nursing infants and its incidence is particularly high in infantile diarrheas, pernicious anemia, various states of colitis, saccharobutyric toxemias and other conditions, hence it may be of no significance at all or be a component of a mixed infection. In ulcerative colitis it is not etiological of the disease except by the way of a mixed infection. It seems to be important in the sense that it is a tissue invader when the hemolytic strepto-

cocci are propagating in the intestinal canal. In such instances it assists in the production of hypersensitivity of the mucosa and in the way is active in the pathology of the disorder.

Under ordinary conditions the pathogenicity of the *Bacillus coli* contained in the intestinal tract cannot be demonstrated or proved. There are certain strains of organisms similar to the *Escherichia* (14) but the limited knowledge concerning them make their understanding impossible. Since these organisms are very common inhabitants of the normal gastro-intestinal tract it is difficult to attach any pathological significance to them, and also many of these organisms found in pathological conditions outside the intestine prove, upon identification, to be harmless as far as the colon is concerned. Under certain conditions the normal intestinal organisms may assume unusual virulence (53) and it is possible that under the influence of the hemolytic streptococci for almost any strain of the *Escherichia* group to become pathogenic by the way of symbiosis and thus be an item of mixed infection (14).

It is possible that various groups of the *Erythrobacillus prodigious* are symbiotic with the hemolytic streptococcus.

The *Clostridium oedematis maligni* is a common denizen of the human intestine and is liable to be found in abundance in the more severe cases of ulcerative colitis. It is probably important not only in the symbiotic sense but also as a toxin producer. As an organism, it has all degrees of virulence and with the other organisms present it is an item in the mixture of infection in preparing the mucosa for pathology.

The bacillus *pypcyaneus* (*Pseudomonas aeruginosa*) is commonly found in the intestine. It, too, is an active toxin producer and when in symbiosis with the hemolytic streptococci and the other mentioned organisms it had approximately the same importance as the *Clostridium oedematis maligni* (the clostridium of malignant edema). It is also possible that its proteolytic enzyme is important by lytic and destructive effects on the colon mucosa. Its numbers are increased in many types of severe gastro-enterological conditions, it is capable of tissue invasion and it is a distinct factor in mixed infections.

The *Clostridium Welchii*, in symbiosis with the streptococci is of considerable importance in the mixed infection. In a smear of normal feces about eight organisms are found in a microscopic field while in some

cases of ulcerative colitis as many as one hundred may be found. Biologically a definite symbiosis between *Clostridium Welchii* and the hemolytic streptococci does not exist, however, when there is a high incidence of the enterococci and a low incidence of the ordinary forms of *Escherichia coli*, the Welchii organisms become a factor with the streptococci (14).

These symbiotic relationships are apparently not of importance as an exciting cause of ulcerative colitis, their importance is in the continuance of the disease and they may be the factor that keeps the primary etiologic factor in activity. Even if this initial etiological organism cannot be demonstrated the infection may continue to exist because of the presence of these normally innocent organisms, for it has been demonstrated that organisms originally mixed with an inoculated infection are able to carry on the pathological process.

It is quite possible that these symbiotic mixtures play a definite role in the remissions and exacerbations of ulcerative colitis. The ratio of organisms in the intestinal tract is constantly changing and as such the "formula" for the mixed infection may be destroyed. It is conceivable that the certain toxic substances are then removed and as such a remission

occurs. When the original symbiotic ratio is reestablished the combined toxins are again able to attack an already sensitized colon and the exacerbation results.

From the preceding material it is seen that the experimental evidence to show the streptococci to be the specific etiologic factor is inconclusive.

Streptococci, indistinguishable culturally from these described as being found in ulcerative colitis, have been isolated from normal stools.

By the use of blood as a culture medium, streptococci are found to multiply and other organisms are destroyed or their growth inhibited. Pathogenicity, then, ascribed to such bacteria as any other organisms normally present presupposes a preceding or primary factor responsible in some measure for this altered characteristic (41).

Logan (32) has shown that by repeated enemas with adequate cleansing agents, the colon may be literally "sterilized" and healing not occur. This would seem to indicate that there were other factors in the etiology of ulcerative colitis.

Symbiotic association of intestinal organisms seem to be an important feature in the chronicity of chronic ulcerative colitis but the part played in the initial infection is not evident.

BARGEN'S DIPLOCOCCUS

In 1924 J. A. Borgen (2) published an initial report of his investigations into the etiology of chronic ulcerative colitis, in which he attributed the cause of the disease to a gram positive diplococcus. His conclusion was based upon the isolation of this organism from the bases of the ulcers in the colon of the patients affected, the production of lesions in the intestine of rabbits similar to those found in the human disease by injection of cultures of the organism and reisolation of the infective organisms, the demonstration of the diplococci in stained section of ulcers from the intestine of the injected rabbit. The organisms were isolated from a large percentage of colons and in smears the diplococcus and gram negative bacilli (the colon bacillus) predominated.

The diplococcus here concerned with is gram-positive, plump and with a tendency to be lancet shaped, quite similar to the pneumococcus except that it has no capsul. It grows on blood agar as an alpha hemolytic streptococcus, and it shows no tendency to form long chains. Identification of the organism was based on the organisms inability to ferment insulin and mannite. This method of isolation was inadequate and by 1937 one

hundred and five different strains were isolated from 266 of 385 patients with ulcerative colitis presenting themselves at the Mayo Clinic. Of these 105 strains of the diplococcus tested, forty one fermented mannite and sixty four did not. These cultural characteristics varied quite frequently for one strain which fermented mannite previous to injection into a rabbit, upon re-isolation from the heart blood might fail to do so (3).

In Bargens first series of experiments, of 190 animals, fifty six developed intestinal lesions. Eleven had been given pure culture of the diplococcus and forty five had received mixed inoculation containing the diplococcus and the colon bacilli. In the latter series 459 rabbits received pure cultures and 131 developed lesions in the colon varying from disseminated sub-mucous hemorrhages to extensive ulcers. In 137 rabbits severe diarrhea was the only manifestation, hence evidence of colonic disease was produced in 268 animals.

The diplococcus has been isolated from foci of infection, apical abscess, and tonsils, cultured and these cultures injected into experimental animals with the production of colonic lesion similar to those of chronic ulcerative colitis. This would lead to the conclusion that foci of infection might be important in bringing about exacerbation of the disease (9).

Cook, working with Rosenow, produced periapical infections in a series of dogs by removing the pulp and innoculating the canal with suspension of Bargan's diplococcus isolated from the blood and mesenteric lymph glands of rabbits in which hemorrhagic colitis developed subsequent to intravenous inoculation of the diplococcus isolated from lesions or foci of patients with chronic ulcerative colitis. Within eight to twelve months later some of the dogs so innoculated developed chronic ulcerative colitis which was demonstrated by proctoscopic examination and by necropsy (4).

An organism, apparently identical with the diplococcus has been isolated by blood culture from fulminating cases of acute ulcerative colitis and at necropsy reisolated from the heart blood. Sections of lesions from the colons of these cadavers showed large numbers of diplococci morphologically similar to these demonstrated in the depths of the inflammatory and granulating tissue from colons of cases of much longer standing (4).

Over a period of years Bargen isolated his diplococcus in pure culture in 189 or approximately 80% of cases of chronic ulcerative colitis. Similar cultures were made of ninety-eight control cases where proctoscopic

examination showed the mucosa to be normal. Diplococci, in some essentials similar to those found in cases of chronic ulcerative colitis, were isolated in sixteen cases. Six strains were agglutinated by immune horse serum developed by repeated injections of horses with small doses of diplococci cultures obtained from human lesions. But four strains produced lesions in the form of a few minute disseminated hemorrhages in the colons of animals injected with the sera. Strains of other streptococci were occasionally isolated, but none produced lesions in experimental animals.

Numerous other writers, Logan (31), Soper (47), MacNaughton (37), Buie (18) and others have likewise isolated the diplococcus described and designated it as the etiologic factor responsible for chronic ulcerative colitis.

Response to therapy has always been of value in aiding a physician in arriving at a correct diagnosis where there is some question which in his mind has remained unsettled. Because Barger believed that he had determined the specific organism responsible for the disease, the use of vaccine or vaccine filtrates was developed by him. The vaccine is prepared by inoculating pancreatic digest broth with pure cultures of the

isolated diplococcus and incubating 48 hours at 37 degrees centigrade. After a thorough shaking to make the mixture uniform it is put up in vials to which is added 0.4% tricresol. This is subcultured to test for sterility. The filtrates are similarly prepared except that the pancreatic digest broth cultures are centrifuged and the supernatant fluid passes through a Berkfeld filter. To this filtrate 0.2% tricresol is added and this is incubated and subcultured as before.

Injections are given subcutaneously, the dosage depending upon the severity of the disease and the tolerance of the individual. The initial dose is 0.1cc and if no reaction occurs the dose is increased, the injection being given every third day to the point of reaction or response in the subsidence of the disease. It is seldom the more than 1.5cc of the filtrate or more than 1cc of the vaccine need be used (3).

The vaccine type of treatment was of particular value in the chronic types of the disease in which the temperature was normal or nearly so, secondary anemia only moderate and the patient with considerable apparent reserve. It appeared to be of no value whatever in the acute fulminating type of disease, a feature probably due to the fact that the patients protective forces are taxed

to the utmost by the infection and further demands on the mechanism of antibody formation go unanswered. (63)

Because of this unpleasant feature passive immunization of the patient with the fulminating case with immune serum as attempted. Rosenow prepared the serum by injecting horses with increasing doses of freshly isolated strains of the diplostreptococcus. After immunization had continued for 2-4 months with dead organism, live organisms were substituted. Bleedings were then taken, the serum removed and after preservation with 0.2% cresol sterility is proved-- It is ready to be given (5).

From 1923 to 1932 inclusive 1348 patients with chronic ulcerative colitis were studied at the Mayo Clinic. In 1923-24 the usual methods of treatment were used. In 1925 the specific vaccine, the preparation of which is described above, was used. In 1927 the use of the serum was begun.

The following table shows the change in the number of patients that came to surgery before and after the advent of the specific type of therapy (6). This table demonstrates the marked decrease in the percentage of operations necessary since the advent of the use of this specific type of treatment and the associated decrease in the percentage of deaths in the patients receiving pure medical care.

	1923	'24	'25	'26	'27	'28	'29	'30	'31	'32	total cases
New Patients.	57	63	102	134	154	189	197	202	140	110	1348
Cases in which ileostomy was performed.	16	13	8	12	3	5	8	2	10	1	78
Postoperative deaths.	7	5	6	5	3	2	6	1	5	..	40
Deaths among patients not operated on.	7	6	6	9	4	4	6	6	2	3	53

There has been much dispute between Bargens and his co-workers and other gastro-enterologists working independently, and very few men have been able to substantiate his work. Bassler (14) believes that Bargens diplococcus is merely a non-pathogenic organism of the enterococcus group, and is normally found in the gastrointestinal tract, and that under certain conditions as previously mentioned--may increase considerably in number. Paulson (37) has likewise isolated this organism from normal human feces. He also believes that the failure of the organism to hold to consistent cultural characteristics demonstrates that no specific organism can be designated as the exciting factor in ulcerative colitis, a fact born out by the presence of numerous numbers of diplococci that present variable morphologic characteristics. Hurst (28) states that Gallart Mones

and Domingo Sanjuan (1935) using the same technique as Bargen, isolated his diplostreptococcus in 32% of cases of ulcerative colitis and in 25% of normal controls, and that the diplococcus produced no more frequent intestinal lesions in rabbits than any other 5 strains of streptococci which they isolated, but they did find that filtrates obtained from cases of ulcerative colitis were more toxic than similar strains than their filtrates isolated from stools of healthy animals. Also Knott found Bargens organism in some of Hursts cases of ulcerative colitis, and noted their presence with abnormal frequency in cases with diarrhea showing no actual colitis, and also often in normal stools.

Paulson believes that Bargens experiments have not been adequately controlled and point out that in his initial report of the diplostreptococci, mixed cultures of the diplococcus and the colon bacillus produced lesions in a larger percentage of rabbits than did the pure culture of the former (40)

Chron and Rosenak (21) in a follow up of 90 cases of ulcerative colitis seen in private practice, who had been treated with retention enemas, intravenous injection of poly-valent antidysentery serum, intravenous typhoid vaccine and miscellaneous methods (auto-

genous vaccines, Bargas's serum, transfusion, routine diet and medication only) respectively, obtained a percentage of cured and improved cases no better than Bargas, and their follow-up period for a fair proportion of their cases (6-14 years) is longer than those reported in Bargas latest three year follow-up. They found that among the various types of intravenous therapy no one item seemed to have a specific effect upon the colitis. It seemed that any protein shock and febrile reaction could bring about a beneficial change in the chronic course of the disease and they believe that best results from Bargas serum were obtained when the serum produced a severe protein shock indicating that the serum acted as a non-specific protein as well as a specific anti-toxin. Their best results followed the use of polyvalent antidysentery serum, and that splendid results were obtained whether or not the blood contained agglutins for dysentery bacilli, although when they were present, the reaction to the serum was particularly fine. Not alone does this serum constitute an excellent non-specific protein, but its late production of serum sickness with urticaria and fever seems to act in its very best manner upon the course of the disease. Paulson (41) likewise is of the opinion that the protein-shock reaction is of value in the management of the disease.

Such is the present status of Bargens diplococcus. In view of the excellent work done by Bargen and his co-workers, and the improved results they have obtained by the use of their serum, it would seem that they have contributed much toward solving the perplexing problem this disease presents. At the present time, no other organized work of such magnitude has been taken along other lines. Because of the conflicting ideas and reports found in the literature at the present time it is impossible to properly evaluate Barten's work. Until further work is done the etiology of this terrible disease will remain a perennial question.

ENDAMOEBIA HISTOLYTICUS

Because of the apparent bacterial type of infection seen in chronic ulcerative colitis, little work has been directed along the idea that the amoeba histolyticus is responsible for the disease. This is due to the marked dissimilarity between the symptoms of the two diseases, the proctoscopic findings, the roentgenologic picture and the ability to isolate the exciting parasite in cases of amebiasis. The rapid response of amoebic dysentery to emetine therapy, and the total lack of any response whatsoever in ulcerative

colitis (20), (51), likewise show the wide separation between the two diseases.

Yeomans (53) mentions amebiasis as an etiological factor in ulcerative colitis but mentions it only in the light that the infestation temporarily reduces the normal body defenses thus allowing secondary invaders of a non-specific nature, which have assumed pathological importance under such a condition, to establish themselves and as such become responsible for the development of an entirely different pathologic picture. Larsen (29) found histories of amoebic dysentery in eight of his series of cases of chronic ulcerative colitis, studied for predisposing factors in the disease. Paulson (41) believes that an infection by *Endamoeba histolytica* may be regarded as a primary factor in some cases and the involvement of ulcerative colitis as secondary, and that those cases of amoebic dysentery, in which, after adequate treatment, the parasite disappears, but the colitis persists, fall in that group.

In a series of 60 cases of chronic ulcerative colitis studied by Winkelstein (51) a small percentage of cases were instances of amoebic colitis. In these cases the organisms were extremely difficult to find. Repeated stool examinations were negative and finally

by using a urinary bladder punched through the sigmoidoscope he was able to demonstrate amoeba in the biopsied specimen. Tollmen (47) working at the University of Nebraska had similar difficulty in demonstrating amoeba in post-mortem material of ulcerative colitis, but finally he was able to isolate them in all of four cases coming to necropsy.

ALLERGIC FACTORS

Attempts have been made to correlate different types of allergy with the onset and recurrences of chronic ulcerative colitis, with the hope of demonstrating particular sensitiveness as being an etiological factor in the disease. Results from such investigation have shown that abnormal sensitization may play an important part in some cases, not only in the initial onset of the disease but also in maintaining it chronically.

Hare (25) studied 38 cases of chronic ulcerative colitis and by special history taking discovered allergic factors in 32 of 35 percent of the patients. In a control series of normal individuals only 26% gave a history of personal or family allergy. In thirteen cases the first attack seemed to be precipitated by some infection of the upper-respiratory tract and of forty relapses--twenty-

one could be ascribed to some upper respiratory infection.

Specific food sensitivity seems to play a great role in some cases. Mackie (34), studying 65 cases of chronic ulcerative colitis, believes that analysis of the causes of exacerbation and recurrence shows intestinal allergy to be important in some instances. It was noted that marked and predictable variations in some patients symptoms would occur following the inclusion or exclusion of certain foods and in many instances changes in the proctoscopic picture would accompany the symptomatic changes. Consequently, a rather prolonged study (1-4 years) was begun. The patients were placed on a modification of the Rowe (44) test meal regime, and were listed as allergic when successive addition and withdrawal of a particular food resulted in predictable change in the subjective and objective phenomena.

Definite clinical evidence of active food allergy was obtained in 33 (50.7%) of the total cases. Fifteen patients gave suggestive but not definitely positive findings and in seventeen cases foods seemed to have no part in the disease mechanism.

Food idiosyncrasies and dislikes were common in the histories of the positive cases and their families likewise had allergic histories, nevertheless many of the positive group were unaware of any food incompata-

bilities until successive test diets revealed their presence and importance.

The sensitivities were not confined to one particular food per patient. As would be expected, the more common foods were the ones producing the most trouble. Twenty six cases showed sensitivity to milk, wheat was an offending food in eleven cases, eggs in eight, and spinach and milk in five each.

During the acute stage of the disease test diets give no indication of food sensitization. In one case, four months after a remission began, a mild recurrence of symptoms was immediately checked by resorting to dietary limitations. The addition of wheat or milk produced an exacerbation of symptoms in a few hours.

Another interesting point is that surgical removal of the grossly diseased portion of the colon appears to modify the pattern and intensity of a patients response to specific foods.

The observation that the patient shows no allergic manifestations during the acute stage is in accord with the general statement that allergic individuals tend to pass through phases of active reaction and phases of reactive desensitization. It seems that the clinical desensitization frequently coincides with

the allergic response to particular foods and is most evident when the early symptoms of recurrence of activity become apparent. (34) This suggests the necessity of carrying out extensive investigations into food sensitivities during the periods of quiescence and when the symptoms are gradually recurring in an attempt to establish or eliminate intestinal allergy as an etiological factor in that case.

DEFICIENCY STATES

It has been noted by Mackie (36) that deficiency states are often found associated with chronic ulcerative colitis. In a series of 75 cases, 47 (62.6%) showed distinct nutritional deficiency states which found expression in atrophy and ulcerations of the appendages of the tongue and Buccal mucous membrane, decubitus like ulcers of the skin, alterations in blood chemistry and the development of peripheral nephritis. He found that these complications would develop regardless of the type of diet, and that particularly anemia would appear even though the diets were rich in the extrinsic factor. Therefore, the defect must lie in insufficient production of the extrinsic factor or in imperfect absorption from the stomach.

Examination of the stools does not show enough alteration in digestion to account for the deficiency.

Brown (17) describes the marked hyperperistalsis of the entire gastro-intestinal tract in cases of ulcerative colitis, food material passing from the stomach to the colon in one hour and reaching the colon in two hours, the peristaltic waves at times being so forceful as to throw the ileal contents 30-40 cm from an ileostomy opening.

Hypermotility, as described above, or decreased absorption from the small intestine might be responsible for the deficiency states in spite of the adequate diets. However, roentgenologic examination of 37 cases (36) showed in 29 subsequent changes in the small intestine which frequently extended from the duodenum to the ileocaecal junction. The normal mucous membrane pattern was destroyed, as though the mucosa and especially the valvulae conniventes were edematous. There was dilatation of the individual coils or groups of coils without evidence of obstruction. There was a disorganization of the normal function and reduction of activity with incoordinate muscular contractions. There were no ulcerations. These changes were consistently present and were most marked in patients with advanced grades of

deficiency disease. The development of these conditions despite a balanced diet suggests that they result from some fundamental disturbance of the physiology secondary to the diseased colon.

Evidence of deficiency disease occurs in the severe chronic types of the disease. When such states appear the symptomatology becomes more complex, the clinical picture more severe and the prognosis.

The clinical pictures suggest that the deficiencies are multiple. Inadequate supplies of vitamin A, B, and B₂ and possibly D, together with the lack of biologically complete protein and erythrocytes appear to contribute to the complex clinical picture to a large extent (36).

Little experimental work has been done along the line of Vitamin deficiencies as might be associated with ulcerative colitis. However, it has been demonstrated that a diminution of water soluble Vitamin B in experimental animals favors atrophy, necrosis and acute colitis but not ulcerative colitis, and it is conceivable that in manna diet deficient in protein and Vitamin B might reduce the healthy resistance of the mucous membrane of the colon to the extent that it becomes susceptible to invading organisms (43).

Since deficiency states appear to accompany the severe chronic types of ulcerative colitis, and show complete absence in other cases it would appear that the factor of deficiency is secondary rather than primary in the disease (36).

PSYCHOGENIC FACTORS

Possible psychologic factors in ulcerative colitis, as introduced by Murray (39), have been mentioned previously in the paper. Bodman (15) puts some cases of ulcerative colitis on functional bases, that they are due to alteration in function of the vegetative nervous system and that the colon is selected "as the battle field on which the emotional conflict is fought out".

Sullivan (48) applied the ideas of Murray to a series of fifteen patients with ulcerative colitis studied over a period of five years. Twelve of the patients were between the ages of twenty and thirty, a period in which the greatest adjustments are made because the individual is called upon to assume adult responsibilities, and he establishes himself both financially and sexually during this period. Most of the patients gave histories of previous bowel disturbances, such as constipation of a spastic type, a tendency to pass two or three soft stools

per day, and the occurrence of loose or diarrheal stools with excitement or emotional upset.

Marked emotional tension seemed present in 66% of the cases and they showed inability to recover from the effects of an emotional episode. Few outward signs of emotional tension could be found and even the usual methods of expression such as anger, despair, triumph, etc., were suppressed. Financial worries, abnormal attachments and particularly marital or sex differences and fears of mother-hood were present in most cases, and following psychoanalysis an amazingly close chronological association between emotional episodes and the onset of the diarrhea was found.

All of the patients were hospitalized for three to four weeks before the emotional problem was found and psychotherapy instituted, during which time they received symptomatic therapy, none of which afforded any appreciable relief and in some cases the condition was even aggravated until the patient decided to talk over the fundamental psychological maladjustment.

The majority of patients submitted themselves to psychoanalysis and accepted the psychotherapy offered. In all cases, when this was accomplished, the diarrhea, and the passage of blood and mucous stopped within a few

days and relief was permanently obtained. Those patients who refused this type of treatment showed no response whatsoever, and all of them had a definite history of emotional imbalance.

The mechanism of such a process is naturally hypothetical, and the mechanism by which the ulcers can be made to disappear by psychotherapy is at the present time a matter of speculation. Sullivan's hypothesis is that the disease is closely related to "neurogenic diarrhea". Emotion, through the vegetative centers in the diencephalon whips the liquid contents of the small intestine into the colon. These enzymes, as has been demonstrated by Brown (17) contain a higher digestive power than the normal intestinal juices. Surface digestion of the colon occurs, bacterial invasion is made easy and acute ulceration occurs. Because the difficulty remains a chronic one, either because the problem cannot be solved or the patient cannot meet the situation, the hypermotility of the small intestine persists and the constant irritation results in chronic colitis. The natural reparative processes of the colon, at times get the upper hand but often fresh emotional disturbances arise and the series of exacerbations and remissions occur. Psychotherapy, by attacking the disease at its

source, solves the emotional conflict, the intestinal motility returns to normal, the chief irritating factor is removed and the colon is now able to handle the bacterial invaders, which promptly disappear (48).

HEREDITARY CONSIDERATION

The part that hereditary plays in any disease of obscure etiology always presents a field for speculation. Hereditary predispositions have been considered as highly important in the etiology of both organic and functional disease. The question of a constitutional inferiority or an hereditary type of mechanism continually presents itself in this disease. The infrequent appearance of ulcerative colitis in more than one or two cases of a family has been noted by Lynch and Felsen (33), Paulson and Borgen (51), and numerous others, which would lead to the conclusion that the condition is not only non-contagious but also shows no hereditary tendencies.

Gutmann, et al (24), believe that hereditary factors may influence the disease on the basis of the transmissability of intolerance to certain substances. In certain families in which they found more than one case they noticed certain sensitivity reactions and also when multiple members of a certain family were allergic to one specific thing they would have diarrhea when they

are in contact with that substance.

A remarkable family in which several members have been afflicted with chronic ulcerative colitis is at present being studied by D. W. Miller (38), who is writing on the possible hereditary factors in the family. Briefly stated the incidence of the colitis in the family may be stated as follows:

An uncle of the present Mrs. Tilse suffered from ulcerative colitis at the age of forty. Mrs. Tilse suffered from intermittent attacks of bloody diarrhea and constipation. Her husband had the condition between the ages of thirty and forty-eight. This couple produced ten children, seven of which subsequently developed chronic ulcerative colitis. Micheal died at the age of fourteen, two years after the onset of the disease. Anna developed ulcerative colitis at eighteen years of age and was treated at the Mayo clinic. She developed a perforation and died of peritonitis at the age of thirty-three. Dutch Tilse gives a clinical history of a mild ulcerative colitis. William developed ulcerative colitis in 1927, evidently following an attack of amoebic dysentery. He was treated at the University Hospital and recovered. Leonard was seen at the Mayo clinic in 1933 showing typical picture of the disease. He did not

respond to treatment and finally died in the University Hospital in 1937--the post mortem diagnosis being Nontropical spru. Alex Tilse underwent operation for his colitis at the Mayo Clinic where a permanent ileostomy was done, which was followed by relief.

Evidently some hereditary factors were at work in this family. For a complete consideration of this family I refer the reader to the thesis by D. W. Miller which may be found in the Senior thesis file in the University of Nebraska library.

Although not of definite consideration in the etiology in the majority of cases, hereditary tendencies may be involved, to considerable extent in a certain minority of the patients.

DIAGNOSIS

The diagnosis of chronic ulcerative colitis is dependent upon four principle factors; history, proctoscopic and sigmoidoscopic examination, roentgenologic visualization of the colon, and laboratory examinations. Clinical diagnosis of the condition is usually attended with little difficulty because of the dramatic and quite typical history given by the stricken patient. The proctoscopic picture is typical of both chronic bacillary dysentery and ulcerative colitis, but the associated

findings usually serve to differentiate these two conditions, if, indeed, they can be said to be differentiated. The radiological characteristics of the disease are almost diagnostic.

History.

The principle symptom that draws attention to the disease is diarrhea, which may begin with the passage of numerous stools containing blood and accompanied by severe abdominal cramps, usually coming on quite suddenly and without a very apparent cause. More rarely the condition may begin insidiously, with a slight looseness of the bowels. The stools then increase in frequency and blood finally appears. The number of stools may vary from six to eight to as many as twenty or thirty in twenty-four hours. Ordinary remedies have little or no effect upon the diarrhea and the patient loses weight quite rapidly and becomes extremely ill. The stools are quite watery and contain only small amounts of fecal material, consisting chiefly of mucous, blood, pus, water, undigested food, bacteria and sometimes fragments and shreds of tissue cast off from the wall of the diseased bowel. The quantity of blood in the stool varies, in some cases it may be considerable while in others it is only occasionally present and in small quantities. It

is usually fluid and intimately mixed with the stool, but it may appear as small clots.

The desire to defecate is sudden and urgent, but the actual passage of the stool is not, as a rule, accompanied by tenesmus unless there is ulceration of the rectum. Frequently there is considerable abdominal pain and tenderness, which, because of its referred nature, is quite generalized.

The progress of the disease varies a good deal and depends upon its nature and extent of the lesions. Most patients, if the actual attack persists, get worse and lose ground steadily from the first and in a few weeks become wasted skeletons. In the more chronic type the condition may continue for months and years, the patient being free from symptoms for variable lengths of time only to have the attacks periodically recur with varying degrees of severity.

The temperature is raised in the acute type and during the exacerbations in the chronic types, sometimes reaching 103° or 104° F. When death occurs it is usually due to exhaustion and general debilitation which cumulate in bronchial pneumonia. If perforation occurs death from generalized peritonitis speedily results. Fatal hemorrhage occasionally occurs (12) (1).

Sigmoidoscopic Picture.

Sigmoidoscopy is the one most important procedure in the diagnosis of ulcerative colitis.

Buie (18) divides the disease into several stages as viewed with the sigmoidoscope. At first a diffuse hyperemia affects the mucosa of the lower bowel, which is more marked near the anus and lower rectum. The upper limit, if it can be seen, appears to fade out gradually into the normal mucous membrane. This stage is followed by an edematous condition of the mucosa, the hyperemia persists, however. The slightest trauma with the end of the sigmoidoscope or even with a cotton swab produces bleeding and mucous membrane is easily broken. Miliary abscesses about one millimeter in diameter appear immediately beneath the superficial layer of mucous membrane. These are diffusely situated throughout the diseased area and have no relationship to the lymphatic follicles. These abscesses subsequently rupture, leaving miliary ulcers scattered over the wall of the bowel which gives it a typical granular appearance. When these spots are wiped off with a cotton swab, the bleeding bases of the ulcers appear as myriads of red spots.

If the disease continues unchecked the ulcers enlarge, necrotic tissue sloughs out leaving shallow or

deep ulcers which vary from a few millimeters to several inches in diameter, the large ulcers being formed by the confluence of smaller ones. The intervening mucosa becomes much swollen and edematous, which may progress to the extent as to form polypoid masses, a condition known as colitis polyposa (16). In severe, long standing cases the entire mucous membrane may be destroyed and the rectum and sigmoid appear to be rigid, constricted tube of pus.

Roentgenologic Aspects.

In the investigation of a colon suspected of being the site of chronic ulcerative colitis best results are obtained by the use of the barium enema. Plates taken following the oral administration of barium are of no value whatever as they merely show rapid emptying time, as in all conditions accompanying diarrhea, without giving a satisfactory idea of the condition of the bowel. For the enema, a fairly fluid suspension of barium is used and is injected slowly, under roentgenoscopic control, careful search being made for any evidence of spasm, irregularities or encroachments on the lumen of the bowel. The behavior of the bowel as the column of barium ascends often gives the first evidence of a lesion. A sufficient amount is injected to

fill the bowel, care being exercised not to over-distend it or cause undue discomfort (19).

As the barium enters the bowel, the filling of the rectum must receive closest attention, because in about 20 percent of cases the disease is confined to this area alone. If the disease is not of long standing there may be no roentgenologic evidence or the only sign may be that of extreme hyperirritability. The patient will not be able to retain the enema long, so violent does the inflamed mucous membrane resent anything in contact with it. Usually the patient will be able to retain it sufficiently long to permit filling of the colon, but by the time a roentgenogram has been made the rectum will have been emptied, leaving the colon filled only above the recto-sigmoid juncture. This gives the characteristic picture: The ampulla, with enough barium adherent to its walls to show its contour, is markedly narrowed and exhibits a series of coarse, linear striations which are shadows of barium retained in the folds of the vigorously contracted bulbous ampulla. As the disease progresses, either with long continuation of the infection or after repeated exacerbations, the characteristic thickening, contraction and shortening take place, and the bulbous shadow of the

normal ampulla may be changed to one which is straight and tubular.

In a typical, well-advanced case one is struck with the rapidity with which the colon fills; the ileocecal valve is reached in an instant, and if the cecum is involved the valve is always patent. The colon itself is small in caliber, and if there is any redundancy, it has disappeared; both the size of the lumen and the length of the colon have been reduced. The course of the colon is exceedingly straight and the angles at the flexures approximate right-angles. From a soft, pliable, thin-walled, greatly winding and twisted tube, the colon has become thick-walled and tense as a sclerotic artery. This picture is not easily confounded with that of any other disease of the colon.

Occasionally one or several contracted areas are seen, giving the bowel the appearance often described as that of a string of sausages. The constrictions may be organic strictures or may be entirely due to localized spasm. Spastic constrictions tend to vary in situation and appearance at different times and are likely to disappear entirely, or at least to diminish in intensity after the administration of a suitable antispasmodic.

Destruction of the mucous membrane, depending on the extent and the depth of the penetration, causes a

varied appearance. If the regions of ulceration are superficial the contour may be entirely smooth, and the outlines of the colon are feathered or furry and appear moth eaten or fringed. If the ulcerations are deep the contour is entirely different; it is rough and uneven, and many niche-like projections are seen extending out from the wall of the bowel.

It is extremely important to bear in mind the occurrence of localized areas of chronic ulcerative colitis in isolated segments of the colon without involvement of the distal segments and rectum (11).

Etiological Diagnosis.

An etiological diagnosis should be attempted in all cases if the physician has adequate facilities for this extensive procedure. Some of the methods of isolation and identification of the infecting organisms have been mentioned and it is not the purpose of this paper to give, in detail, these procedures. They are applicable only to large clinics where special equipment for research is available. However, a diligent search should be made for the more common organisms causing dysentery, particularly if the patient is seen at the onset of the disease.

Investigation should be carried out along all lines and the patient studied from the standpoint of being an individual, not just a segment of infected bowel. The multitude of conditions that may be related to this disease must be carefully considered before being eliminated as an etiological factor in a specific case. Regardless of the possibility of conflicting observations and vague results that will probably be found, this is the only method by which we will eventually be able to develop a clear concept of the disease.

SUMMARY and CONCLUSIONS

1. A small percentage of cases diagnosed as chronic ulcerative colitis are cases of chronic bacillary dysentery.

2. Hemolytic streptococci cannot be assumed to be a primary etiological factor in the production of the disease, but are important in the secondary infection.

3. Bargen's diplococcus is probably a secondary invader and aids in the production of the ultimate pathological picture of some cases.

4. Symbiotic relationships may be established among normally non-pathogenic organisms, resulting in the development of pathological characteristics and the production of toxic substances. These symbioses may be a factor in the persistence of the disease.

5. Cases of amoebic dysentery may become secondarily infected with non-specific organism and ulcerative colitis develop. The amoeba may occasionally be found at biopsy or in the post-mortem specimen of such cases.

6. Ulcerative colitis patients show a high incidence of special sensitivities. Intestinal allergy plays a part in the exacerbations and remissions in some cases.

7. Clinical observation of selected cases shows that functional disturbances may be a factor in producing hyperactivity of the intestine. At the present time the relation of this to chronic ulcerative colitis is purely hypothetical.

8. Nutritional deficiencies associated with chronic ulcerative colitis are secondary to the pathological physiology of the disease.

9. Recent studies show that in some cases there may be an hereditary predisposition to colon infections. This needs further investigation.

10. Experimental results give little indication of a specific type of infection in chronic ulcerative colitis.

11. In a considerable number of cases the presence of infection plus some type of injury to the colon seems to be of importance in the production of the disease.

12. The specific value of specific therapeutic measures is questionable.

13. Chronic Ulcerative colitis presents a quite definite type of clinical, roentgenological and pathological picture.

Ulcerative colitis may be justly called a cosmopolitan disease. Its mystic nature is still the

riddle of the gastro-enterologists. As work is being extended, more and more factors are found which have some influence, directly or indirectly, on the beginning and course of the disease, and from the accumulated work it appears that an ever increasing multitude of conditions bear some relationship to this infection.

In the light of our present knowledge it may be said that chronic ulcerative colitis is a syndrom, for it presents a fairly constant set of signs and symptoms yet no demonstrable specific etiological factor can be found for the majority of cases (41).

The multiplicity of the findings obtained by the various investigators speaks for the non-specificity of the disease and the failure of different men, working with apparently the same technique; to obtain identical results indicates the great variations in the disease from case to case. Each particular case or group of cases will show some variation from apparently similar ones investigated elsewhere.

The failure of response of cases to specific treatment, and a similar lack of response of many cases to non-specific or symptomatic treatment, together with the seemingly miraculous cures obtained by some methods adds to the confusing picture of the disease. As long

as we are unable to pigeon-hole each case according to its etiological nature such conditions will persist. Only after further exhaustive studies of a large series of cases, with investigations directed along all lines; bacterial, parasitic, metabolic, allergic, functional and constitutional, with their proper evaluation, will the etiology of chronic ulcerative colitis assume a rational status and so provide for a rational therapeutic approach.

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