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Chronic ulcerative colitis : with special reference to etiology

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CHRONIC ULCERATIVE COLITIS
WITH SPECIAL REFERENCE TO ETIOLOGY

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Introduction

My interest in the obscure condition known as chronic ulcerative colitis was first aroused during my Junior clinical clerkship. At that time I saw a patient on the Surgical Service who presented a typical picture of ulcerative colitis of two years duration. She had been subjected to a great variety of therapeutic measures during that time, including specific treatment for amebic dysentery and bacillary dysentery, but failed to obtain complete relief. Ileostomy was then being considered, with the plan of subsequent colectomy in mind. The etiology of this condition remained in question, however, and thus shall form the principal subject of this thesis. An attempt will be made to discuss the principal theories of origin which have been brought forth from time to time in the voluminous literature on this subject.

The term chronic ulcerative colitis is used here interchangeably with ulcerative colitis and idiopathic ulcerative colitis, excluding those similar conditions of known etiology: amebic dysentery, acute bacillary dysentery, tuberculous colitis and the colitis associated with lymphopathia venereum.

Chapter I

General Considerations

1. Definition

Chronic ulcerative colitis is a severe noninfectious disease of uncertain etiology affecting individuals of both sexes and of all ages but principally those between the ages of 20 and 40 years. The onset may be acute of insidious with frequent bloody stools accompanied by urgency and tenesmus. It is characterized by an inherent tendency toward spontaneous remission, subsequent relapse and progression. Pathologically the disease results in inflammation and ulceration of the mucose of the colon with progressive production of scar tissue in the deeper layers of the colonic wall. The duration of the disease varies from a few months to many years, resulting in severe disability and a high mortality.

2. Incidence

The incidence of chronic ulcerative colitis seems to be increasing. Whether this is due to better diagnostic methods or actual increase in the number of cases is not known.

At the Mayo Clinic 564 new cases were seen from 1932 through 1935, while from 1936 through 1939 a total of 1,150 new patients presented themselves with this condition (6).

The sex incidence is very nearly equal. Of a total of 592 cases studied by nine authors, 308 were males and 286 were females.

The age of onset varies from early childhood to the seventh decade, but the majority of cases begin between the second and fourth decades.

The question of infectivity or communicability has been raised from time to time but there is no conclusive evidence that the disease can be transmitted to another individual. Cases of conjugal infection are very rare and may well be coincidental (6).

Etiology and Pathogenesis

The etiology of chronic ulcerative colitis has been subject of much protracted debate among those studying the disease. It seems wise, at this point, to emphasize the inherent difficulty in determining the etiology of this condition.

The sex and age incidence help us not at all. The geographic distribution of the disease does not give weight to any particular hypothesis. Perhaps one of the greatest difficulties has been the confusion in the diagnosis of the disease. This is largely due to incomplete study of cases with subsequent hasty and ill-advised conclusions as to the diagnosis. Since ulcerative colitis is also variable in the manner of its onset and subsequent course, another factor leading to confusion with other acute and chronic gastrointestinal diseases ensues. The principal diseases with which it may be confused are bacillary dysentery, amebic dysentery, tuberculous colitis and the colitis of lymphopathia venereum.

Laboratory studies in ulcerative colitis are frequently unsatisfactory. The abundance of the natural floraof the colon, the members of which are normally non-pathogenic, makes for great difficulty in isolation of any pathogenic organism which might be present. The use of direct smears from the ulcerated surface of the colon by means of the proctoscope has been a distinct advance in technique.

The significance of the findings obtained in this manner is open to serious doubt, however, since direct infection of the colonic wall by organisms within its lumen has never been conclusively proved possible. Bargen (3) in his experiments on animals was unable to produce ulceration of the colon by the oral or rectal route with virulent streptococci.

The long search for the etiology of chronic ulcerative colitis has resulted in a large volume of conflicting literature. In order to simplify the presentation of this problem we shall use an outline suggested, in part, by Winkelstein (76) which divides the possible etiologic mechanisms into three catagories:

1. Primary sensitization of the mucosa of the colon by local specific disease or systemic disturbance followed by infection with local or distant organisms or their toxins.
2. A primary functional (neurogenic) disturbance of the bowel which predisposes the tissues to secondary infection.
3. The specific causative organism or virus is yet to be discovered.

Each of the preceding catagories will now be taken up in order and the principal arguments presented.

1. Primary sensitization of the mucosa of the colon by local specific disease or systemic disturbance followed by infection with local or distant organisms or their toxins.

A. Bacterial Infection

(1) Bacillary dysentery

There are two views as to the role of the dysentery organisms in this disease. Some have stoutly maintained that all cases are actually chronic bacillary bysentery, while others have been more conservative and have suggested that only a certain proportion of the cases are due to persistent infection with the dysentery organisms. The second and most prevalent attitude is that chronic ulcerative colitis is initiated by an attack of acute bacillary dysentery which so lowers the defenses of the bowel wall that secondary infection by members of the intestinal flora occurs to maintain the disease.

Saundby (60), in 1906, wasthe first to suggest the possibility that bacillary dysentery is the primary etiology of ulcerative colitis.

He reported one acute case in which positive fecal cultures were obtained for the Shiga dysentery bacillis. This patient showed symptoms and pathology which apparently coincided with those of ulcerative colitis. Since this is a single case, however, and the stool cultures were taken during the first week of the disease, it is very difficult to understand how differentiation was made from acute bacillary dysentery. The only apparent basis for this view seems to be that the case was a sporadic one occurring in a native of England.

Thorlakson (70), stated in 1924 that he believed all cases of chronic ulcerative colitis to be due primarily to the dysentery organisms, followed by a mixed secondary infection, principally by bacillus coli and streptococcus faecalis. That all such cases are due to primary infection with dysentery organisms is untenable since a great many of these patients have no previous history of acute bacillary dysentery. In recent years enough patients have been seen in the acute primary and relapsing stages of this disease in which cultures for bacillary dysentery were consistently negative to make this statement very difficult to prove. (6).

In 1932, Mackie (49) brought forth the view that the Flexner-Y group of dysentery bacilli may cause sporadic cases of dysentery without the presence of epidemic conditions and that some of these cases may become persistent carriers and finally develop chronic ulcerative colitis. He notes that intermittance of the excretion of the bacilli is one of the characteristics of the chronic infection and that repeated cultures are necessary in order to make the diagnosis. That these observations may be correct cannot be disputed.

Hurst (36) and Felsen (32) are emphatic in stating that chronic ulcerative colitis is a form of bacillary dysentery, with or without secondary infection.

Hurst based his conclusions upon the apparently identical pathology in the two conditions and the occasional isolation of the dysentery bacillus from the sesions of ulcerative colitis.

Felsen (32) states, in 1936, that the two diseases are epidemiologically related and that significant agglutination titers for the Flexner organism are obtainable in nearly every case.

Control studies on 300 persons with no symptoms of colitis failed to show significant titers. He claims to have made a diagnosis of chronic ulcerative colitis in 10 per cent of 122 patients with a history of acute bacillary dysentery in the Jersey City epidemic of 1934. He found an incidence of contact infection in his series of 37.4 per cent. Positive fecal cultures were obtained in only eight of the 84 patients studied. Felsen stresses that stool cultures are frequently negative for dysentery organisms in such cases, but that repeated cultures over a period of weeks will increase the number of positive results. His studies suggested that the primary intestinal lesions in acute bacillary dysentery are due to a thermostable endotoxin excreted through the blood vessels of the bowel into the lumen. Lesions have been produced by the injection of the organism into rabbits. The primary pathology described is that of acute bacillary dysentery, which is directly at variance with the findings of Buie (14) in his descriptions of the early pathology of ulcerative colitis. These differences will be fully described in the chapter on pathology.

With the preceding evidence for the etiologic role of bacillary dysentery in this chronic disease

in mind it would seem that the problem would be solved in the control of acute bacillary dysentery. There is much evidence, however, which seriously conflicts with the above opinions.

Felsen (32) has presented no evidence for his contention that the epidemiology of the two diseases is in any way similar. His studies were carried on largely with a special group and did not include patients from other areas. Penner (56) and Hern (35) call attention to the fact that low agglutination titers for dysenteric organisms are not conclusive evidence in diagnosis. Cross agglutinations with other colon bacilli are known to occur.

Paulson (55) reminds us that it would indeed be strange if a severe disease such as chronic ulcerative colitis were caused by an organism which can seldom be isolated from the diseased tissues. The possibility that acute bacillary dysentery may be a predisposing factor in some cases is not disputed.

There are a number of other reasons which make it very doubtful if more than a small percentage of chronic ulcerative colitis cases are due to bacillary dysentery. First of all the acute phase of this disease is seen either at the onset or as an exacerbation following one of the characteristic remissions.

Schlike and Bargen (61) reported a summary on 20 cases of fulminating ulcerative colitis seen at the Mayo Clinic, among which none showed positive fecal cultures for dysentery organisms. These patients were from various parts of the country and all showed the typical proctoscopic findings of the acute phase of ulcerative colitis. Most of them were between the ages of 30 and 40.

Further light may be thrown on the entire situation by stating that there are certain differences between acute bacillary dysentery and ulcerative colitis which make any direct continuity unlikely. Bacillary dysentery is rarely seen in childhood (34), and the majority of cases of ulcerative colitishave their onset in the second and third decades. Bacillary dysentery is frequently a filth disease; ulcerative colitis appears in all strata of society. Furthermore, the large number of cases of bacillary dysentery seen in wartime should certainly cause a great increase in the number of cases of ulcerative colitis if there were any etiologic connection between the two diseases. This phenomenon has not been reported to have occurred following the first World War.

Felsen himself seems to have allowed his judgment to be swayed by a single series of cases since only two years earlier, in 1934, he (31) stated that perhaps a few cases might be due to bacillary dysentery organisms, but that he did not believe that any specific organism was responsible for the majority of cases.

In summation it may be said that nearly all of those who have written on the etiology of chronic ulcerative colitis have come to the conclusion that there are a certain number of cases with a history of antecedent attacks of acute bacillary dysentery, and some in which no such history is obtainable, in which the disease might more properly be termed chronic bacillary dysentery. Recently, Silverman (63) found that in cases of suspected chronic bacillary dysentery where organisms were difficult to isolated agglutination reactions weak, though administration of acidophilus cultures frequently gave good results. He recommends giving one quart of acidophilus milk per day for a period of three weeks. At the end of that time agglutination reactions with homologous vaccine are often strongly positive.

(2) Diplostreptococcus of Bargen

In his studies on ulcerative colitis at the Mayo Clinic, Bargen (3) noticed that the majority of the stool cultures from such cases contained a pleomorphic streptococcus which appeared most frequently in the form of a diplococcus. Using Rosenow's special dextrose-brain broth medium he was successful in growing pure cultures of this organism. This, he postulated, might well be the specific cause of chronic ulcerative colitis. This hypothesis he supported by the discovery of the same organisms in microscopic sections of the tissues of the diseased colon. He found that if pure cultures of this organism were injected intravenously into rabbits, there resulted a hyperemia and edema of the colonic mucosa, with accompanying erosions of its surface and bloody discharge from the rectum. In addition he was able to isolate the organism from the stools of 80 per cent of the ulcerative colitis patients coming to the Clinic and further was able, in some acute cases, to obtain positive blood cultures.

Buie (14) was of the opinion in 1926 that Bargen had unquestionably discovered the etiologic agent of ulcerative colitis.

MacNaughton (51) found pure cultures of a gram-positive diplococcus in six cases of chronic ulcerative colitis.

Bargen (6) has also noted that many patients give a history of an upper respiratory infection, an abscessed tooth, tonsillitis or some other focal infection which was active just prior to the onset of the symptoms of colitis. This he interprets as an argument for a blood-borne initial infection of the colon, followed by secondary intramural infection with the same organism.

If the specific etiologic factor is this diplostreptococcus described by Bargen, then it should show certain constant cultural characteristics. Paulson (55) finds that numerous streptococci as well as the enterococcus may at times, especially in pure culture, take the form of a diplococcus. He believes that it is an error to use the term diplostreptoccus as the identity of a specific organism on the basis of morphology alone. In his opinion Bargen has described a number of organisms with similar morphology but with different cultural characteristics. He has been able to isolate a similar organism from normal human feces as well as from ulcerative colitis.

Futhermore he does not believe that this organism is specific in its ability to produce bowel lesions in rabbits. He was able to produce similar lesions with streptocci from puerperal sepsis and the normal colon, with Bacterium Coli and with the Shiga and Flexner dysentery organisms. Experiments revealed that the presence of blood favors the growth of streptococci more than that of the other inhabitants of the colon. This factor may well result in their predominance in the diseased colon of ulcerative colitis so that they may readily act as secondary invaders of the damaged bowel wall. That there is a predominance of streptococci in all cases is doubtful, however, since Bargen found it necessary to use a special media and a complicated technique in order to isolate the organism.

Bargen (6) differentiates the diplostreptococcus from the enterococcus and Streptococcus faecalis by the differences in the appearance of the colonies on mannite agar, and by the fact that the diplococcus and enterococcus usually do not ferment mannite, while Streptococcus faecalis does. Also, the diplococcus does not grow well on plain agar, while the enterococcus does.

Can we compare, however, the cultural characteristics of two organisms simply isolated from the stools with another which has been subjected to repeated subculture? Changes in cultural characteristics and fermentative reactions are common after repeated subcultures have been made.

Kessel (39) made an interesting comparison of streptococci from the colons of normal patients, and also from cases of ulcerative colitis, with five strains of Bargen's diplostreptococcus. He was able to isolate ten strains of streptococci exhibiting similar morphologic and cultural characteristics. None, however, produced intestinal lesions when injected into rabbits. The species represented were Streptococcus faecalis, mitis and salivarius. He found no one strain associated more frequently with ulcerative colitis than with normal patients. Bargen's strains did not exhibit any apparent differences. Therefore there would appear to be little reason to regard the so-called diplostreptococcus as being essentially different from other types of alpha streptococci commonly recovered from the human gastro-intestinal tract.

The studies of Torrey and Montu (7) failed to reveal any specific serologic type of enterococcus or diplostreptoccus in association with the lesions of nonspecific ulcerative colitis.

That a streptococcus is probably involved in many cases of ulcerative colitis seems to be fairly well established. That there is a specific organism corresponding to that of Bargen is open to serious doubt, however, as may be seen from the evidence given above. May it not be that the primary factor in some cases of ulcerative colitis is an organism, whether streptococcus, staphylococcus or other variety, which is blood-borne from some active focus of infection? Further studies may enable us to form a definite opinion on this matter. It would be diffcult to explain, however, why this mechanism would operate in only a relatively few individuals unless we consider some other factor which would serve to weaken the defenses of the bowel wall.

Bargen has contributed much to the study of chronic ulcerative colitis, whether or not his hypothesis shall prove to be correct. His present attitude (7) in this problem is that the disease is, in many cases, due

to a streptococcus. He no longer insists, however, that a specific strain or type is responsible, but that the disease may be simply a clinicopathological syndrome with a variable etiology and that each case should be carefully studied in order that appropriate treatment may be instituted without delay.

(3) Bacterium Necrophorum

Dack, Dragstedt, and Heinz (22) isolated an anaerobic organism from the isolated colons of ulcerative colitis patients in whcih an ileostomy had been performed. They found that the organism predominated over all others in this situation. Upon repeated search in other cases of the disease they were nearly always successful in demonstrating the presence of this organism. These workers have incriminated Bacterium necrophorum as an etiologic factor in ulcerative colitis on the basis of its presence in the diseased colon and its apparent ability to pass into the blood stream and set up foci of infection elsewhere in the body.

This hypothesis seems to have been received with little enthusiasm since there is very little mention of it in the literature. In 1939 (24) these workers

admitted that the significance of this organism has been difficult to evaluate. They have found it to be associated with any and all lesions of the colon as well as ulcerative colitis. Attempts to produce bowel lesions by injection of the organism into animals have not succeeded. Further studies in 1940 (23) revealed that no specific skin reaction occurs to the intradernal injection of the killed organism in ulcerative colitis patients.

The present statusof this organism seems to be that of an "opportunist" which appears whenever lesions of the colon are present.

(4) Nonspecific bacterial infection

The opinion that this disease may be of variable etiology has been expressed by numerous workers in this field. Paulson (55) does not believe that there is sufficient evidence or properly controlled confirmatory studies which would establish any bacterium as the specific etiologic factor. Logan (43) concluded, from a careful study of 117 cases, that a number of organisms are capable of producing the disease if the body is in a susceptible condition. Kopelowitz (41) asserts that the principal organisms incriminated are

the dysentery bacilli, Bargens' diplostreptococcus, and Bacterium coli. In reference to the latter, however, Nicholls (53) found that hemolytic B. coli could be recovered from cases of ulcerative colitis and from normal individuals in a high percentage of cases. Careful studies fa led to reveal any differences in virulence between the organisms isolated, whether from the diseased or well colon. This would seem to indicate a lack of any special pathogenicity in this organism, but does not preclude a secondary surface infection in the presence of an established ulcerative process.

Winkelstein (76) is of the opinion that a small number of cases are unrecognized cases of amebic colitis. This view is supported by the discovery of amebic cysts in the bowel wall at autopsy in a few cases. Feder (30) found no specific organism in 72 per cent of 88 cases studied in 1938. Mackie (48) and Willard (75) think that ulcerative colitis is the result of the interaction of a number of different factors.

At the present time, then, the general concensus of opinion seems to be that the primary inciting

factors in this disease are extremely variable. Most workers are in agreement that there is present a secondary infection of the ulcerated mucosa which may be a factor in the chronicity of the disease.

B. Deficiency factors

Mackie (50) believes deficiency disease should not be regarded as simply a complication of chronic ulcerative colitis, but as an essential factor in the underlying mechanism of the disease. The appearance of signs of deficiency disease seems to coincide with an increase in the severity of the symptoms and tends to make the prognosis more grave. The role of single vitamins or specific food substances is difficult to evaluate in most cases. There are definite indications, however, that multiple vitamin deficiencies are the rule. The deficiency state is only rarely severe enough to show the classic syndromes associated with the lack of the various vitamins. Evidence of deficiency was found in 62.6 per cent of 75 cases of ulcerative colitis.

From the evidence presented by Mackie it is difficult to evaluate the factor of antecedent vitamin

deficiency. It is conceivable that persons subsisting on borderline diets would show the effects of deficiency early in the disease when the appetite declines. Hern (35) is of the opinion that few of his patients had a significant history of dietary deficiency.

Experiments performed by Verder and Petran (72) using Rhesus monkeys on a Vitamin A deficient diet showed that in the presence of a severe deficiency of this factor, hyperemia of the colonic mucosa and severe diarrhea ensued in two to six months. No ulcerative lesions were observed. This work suggests that vitamin A deficiency might have some predisposing effect, but then, the same mechanism has not yet been shown to occur in the human.

The possibility that dietary deficiency may play a role in the primary etiology of chronic ulcerative colitis cannot be proved or disproved at this time. Studies of the dietary histories of large numbers of colitis patients may, in time, give more definite evidence.

2. A primary functional (psychogenic) disturbance of the bowel which predisposes the tissues to secondary infection.

Many physicians have observed from time to time that many of their ulcerative colitis patients showed evidences of mental aberration during the course of their disease. Many such patients become depressed or show considerable anxiety. They are frequently uncooperative and inclined to be demanding of much attention. This was long considered as a natural reaction to a severe and debilitating chronic disease, although such marked reactions were much less common in other chronic ailments. Little attention was given to the personality and life history of the patient, thus practically nothing was known of his mental status during the years before he contracted chronic ulcerative colitis.

Sullivan (69) reports that psychogenic factors are very frequently associated with the etiology of this disease. He calls attention to the fact that the great majority of cases are between 20 and 30 years of age, at which period in life most persons must assume adult responsibilities. In his opinion about 75 per cent of cases of chronic ulcerative colitis are of psychogenic origin.

Wittkower (77) found evidence of psychological abnormalities and disorders far beyond the range

of individual differences which antedated the onset of the disease in the majority of the patients studied. In many cases the history of previous nervous disturbances could be received by interviews with relatives of the patients. The patients themselves commonly believed the onset or relapses to be the result of worry.

The experience of Daniels (26) has likewise observed that many cases of ulcerative colitis shown very definite relationship to emotional difficulties and that improvement in the condition frequently results from resolution of conflicts.

Schlicke and Bargen (61) in a study of 20 patients with fulminating ulcerative colitis noted that one half of those who died had suffered a period of severe nervous stress coincident with the onset of the disease. Nearly all of their patients were tense and nervous and tended to be uncooperative.

Many authors have attempted to formulate a particular personality type which would be especially likely to be susceptible to attacks of this disease.

Brown (13) found that the majority of his patients were characterized by a tendency to give up in the

face of difficulty. This finding has been supported by the observations of Sullivan (69).

Another characteristic appears to be the inability to make adequate adjustments to adult life. In Brown's group of 30 cases there was not a single successful marriage. None of the males in Murray's original series were married. This was attributed to a conflict between mother-attachment and the desire for marriage. Many patients show an abnormal emotional attachment to the mother or some other close relative and a definite tendency to narcissism.

The fear of pregnancy and childbirth is believed to be a frequent precipitaing factor in women (27,28).

Alexander (1) called attention to the symbolic use of feces at times as a gift, at other times as an expression of hostility, varying with the degree of regression.

Crohm (20) reported the case of a 16 year old girl who developed the typical symptoms and protescopia findings of the acute phase of ulcerative colitis following criminal rape. Her symptoms subsided after a course of sulfasuxidine.

A careful psychiatric study of 40 patients was made by Wittkower (77). He was unable to place these

people in any single psychological group, but found that 35 of them could be divided into three groups:

Group I - 17 patients

Overconcientious and overscrupulous as children
Many showed grossly abnormal attachment to one parent
Relatively few were married
Moral code very rigid
Most showed obsessional thoughts, fears and actions

Group II - 12 patients (all women)

Excitable and openly emotional in childhood
Dramatic, emotionally labile
Superficial and labile interests
Very few real friends, but mix easily
Incapable of loving deeply because of their own deep love of themselves
Undue, often ambivalent attachment to one parent
5 out of 12 showed gross hysterical symptoms

Group III - 6 patients

Quiet, unassuming behavior in childhood
Social anxiety
Shy, quiet, depressed

In 28 out of the 40 patients there was an immediately antecedent emotional upset serious enough to be considered the precipitating factor.

The following are some of the most frequent personality characteristics found by various other workers (52, 27, 25, 1)

Emotional immaturity
infantile response to fear
emotional tension
fear of failure of achievement
passive-receptive claims to be loved
extreme neatness
money-feces equation
overly aggressive
low energy endowment
financial difficulties

The literature on the psychogenic aspects of this condition does not give us sufficient reason to indict any one personality type as being predominantely present. We must, of course, realize that many of the characteristics found in these patients could also be found in any similar group taken from the general population if equally extensive probing into life histories were carried out. There must be some significance to the high concentration of abnormal characteristics in such small groups, however, and further studies are certainly indicated (68).

In order to be of significance in etiology, psychogenic factors must antedate the onset of the disease or one of its exacerbations, since any severe andprolonged ailment may bring out latent neurotic traits in persons who, under normal conditions are quite stable. Recovery and convalescense may be seriously

interfered with, however, by neurotic manifestations appearing during this disease (78).

Care should be taken that mentally traumatic episodes are not incriminated without proper evaluation of the reactions of the patient to them, since not all of us react alike to similar unpleasant occurrences in our lives. Where one person may adjust quickly to a difficult emotional situation, another reacts with neurotic symptoms. Neither must it be assumed that because they are not superficially evident, there are no emotional difficulties present. Such problems tend to remain in the background in the presence of severe organic disease and careful study may be necessary to bring them out (78). Certainly it would be wise in view of the present status of this problem to carry out personality studies on all patients who present themselves with this disease (68).

There has been no attempt to claim that chronic ulcerative colitis is caused directly by the factor of emotional trauma or long continued stress, but there are definite indications that such conditions antedating the onset of the disease may act as potent precipitating factors. This implies that there may

be, as a result, some neurogenic disturbance of the bowel which would make it susceptible to attack by organisms from foci of infection or perhaps from those present during an upper respiratory infection.

Yoskin (78) states that the diencephalon may act as a mediator in the transferance from psychic disturbance to gastrointestrial dysfunction by reason of its being a center for several related functions.

Sullivan (69) has suggested a working hypothesis for the mechanism of the psychogenic causation of ulcerative colitis. He postulates that it may be possible that emotion, operating through the vegetative centers in the diencephalon, causes increased activity of the small intestine, thus emptying its liquid content prematurely into the colon. He would account for the production of ulcers by suggesting that partial digestion of the ulcers by suggesting that partial digestion of the colonic mucosa may occur due to abnormally powerful enzymes or to a heightened susceptibility to the mucosa to normal enzymatic action followed by bacterial infection, which causes the actual ulceration.

While there is some evidence of a derangement of the function of the small intestive, there is nothing at present to support the contention that there is surface digestion of the mucosa in the early stages of ulcerative colitis.

There is one condition, known variously as "mucous colitis" or "irritable colon" which is known to be of psychogenic origin. The condition is characterized by the passage of loose stools containing varying amounts of mucus at times of emotional stress. There are no changes in appearace of the colon during the attacks and ulceration does not occur. Although a similar mechaism seems to be a possibility in this condition and in ulcerative colitis, the patient with "mucous colitis" never becomes a victim of the more severe disease. The reason for this peculiar situation has never been satisfactorily determined.

It is well known that there is hypermotility and spasticity of the colon in ulcerative colitis. This is evident on radiologic study and from the complaints of cramping pain and urgency by the patient. That this mechanism might have something to do with

the ulcerative process was first suggested indirectly by Virchow (73), in 1853, who noted that the projections of the mucous membrane seemed to be affected first, and that these susceptible areas lay over the insertion of the three longitudinal muscle bands of the colon and on the transverse folds of the mucosa.

This feature of the disease was also described by Hern (35), who states that at autopsy nearly every case shows a longitudinal arrangement of the ulcers and that in some the position of the tenial bands is obvious from the position of the overlying ulceration.

Lium and Porter (45) in 1939 studied six cases of chronic ulcerative colitis at autopsy. The duration and severity of the disease varied. Stool cultures and agglutinations were absent in all. In every one of these six cases the ulcers were arranged longitudinally and directly over the tenial bands. Intervening ulcers were at right angles to the tenia. The authors concluded that since the tenia are the most powerful muscles in the colon that there might well be a direct relation between the muscle and the lesions. The early changes noticed in these cases

were hyperemia, edema and petechial submucous hemorrhages. A peculiar feature was the nearly complete absence of mucus from the epithelial cells in the early stages.

In order to supplement these interesting findings Lium (44) excised a short section of the colon from a series of dogs. The colonic sections were split and the now rectangualr pieces sewed into the abdominal wall, replacing similar areas of full thickness skin. The exposed mucosa was then covered with gauze dressings to protect it from drying and irritation. Control studies showed that the protection thus afforded maintained the normal histologic features of the mucosa.

The explants were then subjected to severe muscular spasm by giving prostigmine intravenously and acetylcholine salt locally. The first changes noted were hyperemia and edema. Shortly petechial hemorrhages appeared beneath the surface epithelium, followed by superficial erosions, oozing of blood from the surface and induration of the explant. Microscopically the appearance was that of a diffuse inflammatory reaction in the mucosa. It is interesting to note that the mucus had disappeared from the goblet cells

in the areas subjected to severe muscle spasm.

Plium believes that from the resultsof these experiments, the conclusion may be drawn that intense muscular activity of the colon is capable of producing damage to the mucosa which resembles the early pathology of ulcerative colitis. He thinks it highly probable that ulcerative colitis is primarily a disease caused by muscle spasm and hypermotility of the colon and that infection, when present is a secondary involvement.

Naturally, no definite conclusions can be drawn from experiments on animals since there is no guarantee that similar conditions in man would give eqivalent results. Since such direct experimentat ion cannot be done in man we shall have to await the outcome of less direct investigations before making assertions as to the importance of intense muscular contraction in the etiology of the disease.

Another interesting sidelight on this mechanism has been brought forth by the preliminary studies by Lium (46) on the reactions of the rectal musculature to distention. A rubber balloon filled with water under controlled pressure was inserted into the rectal

canal in eight normal subjects and in one patient with ulcerative colitis. Studies of the contractions resulting from distention of the rectum with intermittent injections of water into the balloon showed that in the normal subjects there was first an increase in tonus as a local response to distention and then further contractions of the rectum between injections. The latter reaction was interpreted as a spinal reflex since it disappeared when the subjects were given spinal anesthesia. The response in the ulcerative colitis patient was much more severe and prolonged and spinal anesthesia failed to eliminate internal contractions. Thus there appears to be an independent ability of the musculature to respond strongly to local irritation which may have some bearing on the chronicity of this disease if muscular spasm does actually produce damage to the mucosa.

From the evidence so far available it seems apparent that psychologic and neurogenic factors play a definite part in the onset and course of chronic ulcerative colitis. The true evaluation of their role in its etiology will necessarily have to await

the results of continued investigation in this field. Perhaps we may conclude, however, that it is in the best interests of the patient to make a study of his personality and of the specific problems with which he may be struggling in order that his treatment and convalescence may be facilitated.

3. The specific causative organism or verus is yet to be discovered.

Chapter II

Pathology

Pathologically this disease is characterized by extensive inflammation and ulceration of the colon. The disease usually begins in the lower rectum but may spread upward by continuity to include the entire colon and, at times, the terminal ileum as well. The severity of the disease cannot be cofrelated with the extent of the lesions.

Initially the ulcers are small, circumscribed and superficial, with well defined edges. As the process continues the ulcers become larger by means of necrosis of the surrounding mucosa and may become confluent in some areas. They are somewhat undermined but not as extensively as in amebic dysentery.

The pathology of chronic ulcerative colitis varies with the stage of the disease which is present at the time of the examination. Because of this variation there is some difference in the descriptions found in the literature. It is quite possible that all of the stages of this disease have not as yet been completely described. It is characteristic that in this disease

the patient seldom seeks medical advice until the condition is rather far advanced; thus much more is known of the more chronic stages. Bargen (6) and Buie (14), however, have studied a great number of fairly early cases proctoscopically at the Mayo Clinic. These workers have described a form of ulcerative colitis which they believe to show consistency in pathology and possibly in etiology. They advocate the name "thrombo-ulcerative colitis" for this disease.

Buie (14) believes that there are four rather well demarcated stages which may be differentiated by proctoscopic examination.

The first consists of a diffuse inflammatory reaction or hyperemia beginning in the lower rectum and spreading upward. There is no definite line of demarcation between normal and involved mucosa; the latter fades gradually into the former. More careful inspection of the surface reveals numerous small hemorrhages scattered about the hyperemic mucosa.

The second stage is less well defined and apparently transitory, since it is seldom seen at autopsy.

It is marked by a diffuse edema of the involved region. The mucous membrane appears thickened and red and is now exceedingly friable; the slightest trauma being sufficient to cause bleeding.

As the disease progresses small yellowish spots appear directly beneath the mucous membrane causing little if any elevation of the mucosa. These tiny abscesses are scattered diffusely throughout the involved portion of the colon, and constitute the third stage. Bargen emphasizes that the lymphoid tissue of the colon is not involved in this process. Since this finding sharply differentiates this condition from acute bacillary dysentery, in which the lymph follicles are involved consistently, it appears certain that the acute onset of ulcerative colitis is not identical with the former condition.

Rupture of the miliary abscesses through the mucous membrane brings us to the fourth stage; that of ulceration. It is important to remember at this point that these stages are seen in their characteristic form only in the initial attack of the disease. During an exacerbation following a remission, only those portions of the mucosa not previously scarred and ulcerated will

show the various stages (6).

The chronic fibrotic colon which is seen in the disease of long duration may well be termed the fifth stage.

These stages have not been seen uniformly by most investigators since many of their cases were of long duration when first examined. When extensive fibrosis and destruction of the colonic wall has occurred there is very little normal mucosa left, thus the early stages of the disease are past or are present only in scattered areas of the remaining mucosa.

The following description by Bargen (6) of the early microscopic findings in ulcerative colitis corresponds largely with the early stages seen proctoscopically by Buie (14):

> The earliest microscopic changes recognized in the wall of the colon are small lesions associated with edema and hemorrhage. These are often roughly pyramidal. The capillaries of this region are dilated and packed with erythrocytes. Some of the erythrocytes seem to have spread throughout the adjacent tissue, giving the appearance of a red infarct. At the base of this region, deep in the mucosa and submucosa, capillary vessels are occluded by tissue debris. These capillaries seem to originate from occluded vessels deeper in the tissue, and finally distinctive branches of blood vessels, filled with homogenous thrombi,

> can be made out. The limiting membranes of the surface of the mucosa may be intact at this time, and this gives the impression that the initial disease originates there and not through some material introduced from the lumen of the bowel, which has caused abrasion and necrosis of tissue. At about this stage of the disease numerous diplostreptococci are domonstrable in the intestinal wall. From this it is understood that these infected infarcts might result in minute abscesses; hence, in the third stage of the disease they appear as minute, roughly pyramidal regions of necrosis surrounded by hemorrhagic zones. In the necrotic center lie many polynuclear cells in a mass of disintergrating tissue and the limiting membrane is covered with exudate.
>
> The thickness of the wall of the bowel, noted grossly, is striking microscopically. Through it there will appear diffuse infiltration of lymphocytes and plasma cells.

As the disease progresses the submucosa becomes thickened and fibrosis occurs. The wall of the colon becomes contracted and multiple strictures may result. The colon is shortened as well as contracted by this process, so that in advanced cases it takes on the appearance of a horseshoe, all flexures having disappeared.

Numerous attacks as well as the protracted course of the disease result in the loss of most of the mucosa

of the large bowel. The occasional remaining mucosal tags take on the appearance of polyps. The colonic wall in the late stages is frequently very friable and great care must be taken that it is not punctured during a proctoscopic examination.

There are a certain number of cases diagnosed as chronic ulcerative colitis in which the above pathological description is not seen in its typical form. Many of these cases were probably initiated by amebic or bacillary dysentery.

Chapter III

Diagnosis

1. Symptomatology

The symptomatology of chronic ulcerative colitis is somewhat variable, depending upon the type of onset and the severity of the disease.

In approximately one-half of the cases the onset may be said to be indisious. The disease begins with one or more bloody stool without other apparent symptoms, As the conditions progresses, pus and mucus appear in the rectal discharges in varying amounts. Pain may or may not be a prominent symptom in chronic ulcerative colitis. There may be intermittent cramping sensations in the abdomen and there often is considerable distress,from gas. In some cases there is much griping and tenesmus with each of the frequent stools. The pulse rate is usually increased and is of prognostic importance. Patients with a rate above 120 seldom survive for long. This finding apparently indicates a severe lesion in the upper colon (35). Nausea and vomiting may occur in cases showing considerably toxemias. The subsequent course of the disease may be mild throughout or may increase gradually in severity

with increasing frequency of stools, cramping abdominal pain, tenesmus and general malaise. In this form there is tendency toward frequent remissions of variable duration. In some cases the patient will have two or three attacks each year. In others the disease tends to decline in severity with each exacerbation and may eventually disappear. In still others there is steady progression in severity with each new attack, with death in a fulminating episode the final result.

In the remaining group the onset may be severe or even fulminating. Here we see a sudden severe dysentery, at times very violent, with bloody, purulent stools, a septic fever, malaise, anemeia and great loss of weight (61). The number of stools in more severe cases may range from ten to thirty a day until the patient is finally almost exhausted as a result of the pain, mental anguish and the uncertainty of his state. The fulminating cases may progress very rapidly, death occurring in two or three months. In some of the severe cases, however, there may be complete recovery in a few months (6).

Strauss and Strauss (66) believe that the type of disease may be correlated with the extent of the

pathology in the colon. The mild form of the disease being characterized by superficial involvement of the mucosa alone, while in the severe type all the layers of the colonic wall show infection and destruction with infiltration of the mesenteric lymph nodes.

The apparently inconsistent character of the symptoms and course of this disease have led some to believe that there might be actually two separate conditions, one chronic and the other acute. In view of the frequent fluctuation in type which often occurs in the same patient, it would seem rather that we are dealing with different phases of the same disease process.

2. Proctoscopic examination

Careful examination with either the proctoscope or the sigmoidoscope should be a routine procedure in every case of ulcerative colitis in which they can be safely used. The usual findings have been described in Chapter II.

3. Laboratory findings

Repeated cultures, both of the stools and from

material from the bases of the ulcers should be taken in order to rule out bacillary dysentery and to determine which organism may be incriminated as a secondary invader.

The blood picture in ulcerative colitis is usually characteristic. There is little or no increase in the number of leukocytes buttthere is a definite shift to the left in the differential count. Late in the disease there is a well marked hypochronic anemia, which often proves refractory to treatment with the usual iron preparations.

The erythrocyte sedimentation rate is always increased in this disease. Not uncommonly it will range between 50 and 150 millimeters in the first hour, giving evidence of the severe destructive process.

4. X-ray examination

In early cases X-ray examination of the colon may reveal some loss of haustration and in some cases mucosal defects representing ulcerations. In more advanced cases all evidence of haustration may be gone, leaving a contracted tube-like colon. The

longitudinal extent of the ulcerative process can be determined roentgendogically. The normal sections of the colon show the usual haustral markings and the usual diameter of the organ is preserved. Fluoroscopic examination reveals a very rapid filling of the entire colon with barum while the enema is being given. Proctoscopy is of more value in differential diagnosis than is roentgenography. Double-contrast films are the most useful for the examination of mucosal markings.

5. Differential diagnosis

(A) Bacillary dysentery

Repeated stool cultures in the first two weeks of the acute phase of the disease will usually be sufficient to discover cases of the disease. The history of a local epidemic of bloody diarrhea is of significance. Prostoscopically the disease cannot be differentiated from ulcerative colitis with any degree of certainty. The incubation period is usually from 12 to 48 hours (32).

(B) Amebic dysentery

The symptomatology of this disease is very

similar, in most cases to that of ulcerative colitis. Careful examination of material from the stools should be used to concentrate the fecal discharges to find the cysts of endaneba histolytica. Proctoscopic examination reveals numerous deep ulcers with overhanging edges. The mucosa is not diffusely hyperemia is in ulcerative colitis but is only so affected for a short distance surrounding each ulcer.

(C) Tuberculosis colitis

There is usually little difficulty in finding concomitant chest lesions in such cases. The stools are not characteristic but often there is alternating diarrhea and constipation. There is seldom any gross blood in the stools. The diagnosis may often be made on history and exclusion of other recognizable conditions. The proctoscopic appearance is very similar to that seen in amebic dysentery. Peyers patches are uniformly involved in this condition.

(D) Lymphopathia venerum

Frequently in this condition there is a history of inguinal glandular enlargement. The best method of diagnosis is the free intradernal test which is only positive in those having or having had the disease.

Chapter IV

Complications

No attempt will be made here to enter into the prolonged discussion which would be necessary in order to fully evaluate the importance of the numerous complications of ulcerative colitis.

Bargen (39) has found 268 complications in a series on 693 patients. Polyposis was the most frequent complication, which was encountered in 10 per cent of the patients in this series. Bargen and Comfort (10) believe that this condition is a result of the inflammation and irritation occurring in the bowel wall. In ulcerative colitis these polypi actually seem to represent the islands or tags of mucosa which are isolated by surrounding confluent ulcers. Subsequent irritations with proliferation of fibioblasts result in rounding of the mass with pedicle formation. The condition appears to increase the severity of the disease.

Stricture is the complication second in importance. This condition occurred in 8.5 per cent of Bargen's series. Not infrequently these will be a

severe stricture of the lower rectum which makes the introduction of a proctoscope impossible. Strictures appear to be due to unequal contraction of scar tissue in the badly damaged colonic wall. They are especially important as causes of obstruction to the fecal stream and in that they may cause the formation of large pockets of pus in the dilated portions of the colon.

Another serious complication or sequel to this disease is the retardation of growth and sexual development which has been observed in cases in which the onset occurred during childhood (12). The exact mechanism operative here is not known but probably is connected with severe nutritional deficiency during the developmental years.

The less frequent complications seen are: arthritis, peurectul abscess, skin lesions, renal insufficiency, endocarditis, splenomegaly, perforation, malegnant disease, ocular disease, fatal hemorrhages and renal calculi. The exact relationchip between some of these complications and ulcerative colitis is not clear. In some cases there seems to be a definite connection and in others the findings may will be concidental.

Hemorrhage and perforation are, of course, the most dangerous to life itself but are not very frequent, being found in 0.4 and 2.6 per cent of the patients in Bargen's series of 693.

Vitamin deficiencies appear to be rather common, especially late in the disease (13), and should be combatted by the provision of supplementary concentrates as indicated.

Chapter V

Treatment and Prognosis

Treatment

1. General Considerations

The art of Medicine is nowhere more important than in the treatment of chronic ulcerative colitis. This disease so frequently leads to chronic invalidism that any measure which may add to the comfort of the victim should form a legitimate part of the treatment in any case. It is, in part, for this reason that carefully controlled studies of various suggested therapeutic regimes have been so difficult to carry out. One hesitates to limit the treatment to any one therapeutic agent for fear that the exclusion of others may jeopardize the chances of recovery.

Since chronic ulcerative colitis is characterized by sudden spontaneous remissions and sudden severe exacerbations, great care must be exercised in the interpretations of therapeutic results. It becomes obvious, then, that any new treatment must be used in a large number of patients in the same stage of the disease and rapid and striking improvement must occur in the majority of cases before conclusions may be drawn as to the efficacy or failure of the

treatment (76). There are, perhaps, few diseases in which so many types of treatment have been used; some with apparently miraculous results. It is in just such instances, however, that we find conclusions based on a series which is far too small to be of any significance. There are also those authors, exemplified by Bargen, who have used "specific" serum or vaccine therapy in large series and claimed very good results. Other investigators, however, have repeatedly shown that comparable results may be obtained with any form of protein shock (55).

2. Medical therapy

(A) General

In general the treatment of ulcerative colitis must be adjusted to the needs of the individual patient. Where dehydration is marked, fluids by vein are often indicated. The basis for treatment in most cases is a high-calorie, high-vitamin diet (59), bed rest during the severe stages and judicious psychotherapy throughout (48, 13). Blood transfusions are very valuable in debilitated patients and may prove to be a life-saving measure in some cases. Sedatives and opiates are frequently helpful

in patients who find it difficult to obtain rest during the night because of abdominal pains or the persistent urgency (75, 67, 40). Colonic irrigations are no longer considered advisable in this disease since in most cases it results only in greater irritation of the mucosa (75,48). Some have maintained that colon lavage gave good results, however (33,65). Burnford (15) recommended local treatment by ionization with two per cent zinc sulphate. No definite conclusions are warranted as yet however. Cheney (18, 19) has used liver extract and Vitamin B-1 in a small series and has obtained good symptomatic relief. He believes that there may be some unidentified factor in liver extract which would increase the resistance of the mucosa to ulceration.

(B) Vaccines and sera

Bargen (5,6,8,9) has been the great exponent of the use of "specific" vaccines and sera. Since he believes the etiology of the majority of cases to be the so-called diptostreptococcus, he has prepared several different vaccines and has claimed very good results with them. In an evaluation of serum therapy in 181 patients, Simpson and Bargen (64) found that

about 13 per cent obtained complete and prompt relief of all symptoms; moderate to good response in 64 per cent and slight or no improvement in 26 per cent.

In other hands, however, this treatment seldom gives significant results. Paulson (55) and Bassler (11) have suggested that much of this success has been due to a non-specific protein shock reaction. This is supported by the good results obtained by many with anti-dysenteric serum (31, 75) and the equally good results obtained by Schwartzman and Winkelstein (62) with antitoxic, anti-B-Coli serum.

Various authors have noted one peculiar fact which must be kept in mind in attempting to evaluate any form of treatment for ulcerative colitis. About 75 per cent of these patients will either become well and remain well or will show a remission after a certain interval of time on any form of therapy that has been devised so far.

(C) Sulfonamides

The advent of the sulfonamide group of drugs aroused the hope that here might be the treatment which would be effective in ulcerative colitis. Bargen (6) used neoprontosil in a number of cases and reported encouraging results. Rodaniche, et. al. (57) reported

the effect of sulfadrazine, sulfathiozole, sulfaguanidine and sulfasuxidine on the bacterial flora in the stools of ulcerative colitis patients. They found that after two to 14 days the coliform organisms greatly decreased or disappeared, while the streptococci and staphylococci greatly increased. There was practically no effect on the course of the disease Crohn (20) reported the use of sulfasuxidine in 28 cases with 17 "cured" or improved and 12 unimproved or worse. Bargen (4) obtained good response in 26 of 37 patients on sulfathalidine and found few serious reactions to the drug itself.

Apparently, then, the status of the sulfonamides in ulcerative colitis hangs in the balance. They certainly do not appear to be of any striking benefit but may prove a valuable adjunct to the treatment of this disease.

3. Surgical therapy

The surgical treatment of ulcerative colitis has undergone considerable change in the past few years. Earlier workers believed that colectomy would be preferable but that it was far too dangerous

to be of practical importance. In 1920 Lockhart-Mummery (42) strongly recommended the operation of appendicostromy to allow through and through irrigation of the diseased colon. Many others, however, have come to the conclusion that this procedure is of no use, since the initial mortality was often high, the bowel opening frequently closed of its own accord and improvement was seldom noted. Jones (38) recommends a wise combination of medical and surgical treatment and advocates the performance of an ileostomy or colostomy for stricture, neoplasm, polyposis, peurectal abscess and regional or right-sided colitis. Cave (17) believes that operation becomes elective when the colon has become a fibrotic, narrowed and useless organ. He recommends ileostomy followed by subtotal colectomy and eventually a proctectomy. In a series of 40 cases, his surgical mortality rate was 22.5 per cent. Cottell (16) believes that colectomy is indicated after ileostomy in about one-half of the cases operated. The most frequent factors in this decision are medical failure and stricture of the colon. Strauss and Strauss (66) think that ileostomy should be performed as soon as the

diagnosis of ulcerative colitis has been made. A simple loop ileostomy is recommended. They believe that medical treatment has very little value.

Prognosis

The prognosis for life in this disease is not at all bad. Bargen and Buie (9) in a review of 1,348 patients found that 898 were free of symptons and only 132 or 10 per cent were dead. The disease is nevertheless a cause of chronic invalidism and as such the prognosis is serious in many cases. Remissions are very common in this disease and as a result statistical studies have very little real value unless they are made on patients who have been followed closely for many years.

The best method of insuring a reasonably good prognosis in ulcerative colitis consists of thorough diagnostic study, individualized medical therapy and appropriate surgical treatment as indicated by the subsequent course of the disease.

Discussion

Although chronic ulcerative colitis might well be called a clinicopathological syndrome rather than a disease entity, the latter seems useful for the purposes of discussion at the present time. Perhaps it has been a part of the persistent tendency to please all clinical disorders in one "pigeonhole" or the other which has resulted in so much confusion in the naming and classification of this condition. There are many who think it best to study each case carefully in a sincere attempt to discover all probable etiologic factors and to base the treatment upon the findings obtained. This appears to be the only rational attitude in the face of the many variations in form, symptoms and course which are so evident in ulcerative colitis.

There is no one causative factor which may, at present, be incriminated in the etiology of this disease. The most likely possibility at this time would seem to be that the condition is caused by the interaction of a number of factors. The influences of constitutional predisposition and psychologic conflict cannot be lightly dismissed. Although no single "type" can be evolved which would be more susceptible to this

disease than another, there should be no sense of failure since man is notoriously difficult to classify in any such manner. The part played by bacteria in this disease remains in the realm of speculation. Focal infection or a transient bacteremia may prove to be of prime importance, since the greater amount of evidence is in favor of a blood-borne mechanism in the infection of the colonic wall.

The treatment of ulcerative colitis must remain on the basis of careful evaluation of the needs of each patient, good common sense and the response to therapy. The latter, however, must be used with much discretion. The high frequency of spontaneous remission, with or without adequate treatment, should be sufficient to remind us that the evaluation of treatment requires long periods of observation.

Through the medium of modern medical therapy the majority of the patients afflicted with this disease can be made comfortable and many of them enabled to return to a productive life with a reasonable degree of good health.

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