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CHRONIC ULCERATIVE COLITIS
With Special Study of Etiology

Albert P. Graham

1931

CHRONIC ULCERATIVE COLITIS

With Special Study of Etiology.

The damage done by this disease, the poor prognosis and the unsatisfactory management and treatment has led to considerable amount of study by investigators in recent years and the literature seems to indicate that their efforts have not been entirely fruitless. In my survey I find that it is generally agreed that chronic ulcerative colitis is a disease which gives a typical symptomatic proctoscopic and roentgenographic picture. The etiology is not proven conclusively although Bargen through an immense amount of investigative work at the Mayo Clinic thinks the disease is due to a definite diplococcus, and most authorities concede it to be infectious in origin. Medical treatments vary greatly and hence none are very effective. Probably vaccines offer the best aid in treatment. In the pages which follow I shall present the work and ideas of recent investigators.

SYMPTOMS:

Logan ⁶⁰ describes the condition as follows: The disease begins practically always with dysentery, either starting gradually and becoming more severe, little attention often being given it at first, or coming suddenly as severe diarrhaea. It may develop as an isolated case or as one of a number

of cases in which the patients are similarly affected by diarrhoea, all the others clearing up in a short time and this patient tho treated exactly like the others by the same physician failing to get well. The diarrhoea is at first watery, later the stools usually contains some fresh blood and pus. The number of stools varies from 2-3 up to 15 daily, which may keep up for several years, or the ulcers may become latent similar to duodenal ulcers, and during this latent period, the bowels may become regular or constipated. As the rectum is most severely involved, tenesmus is often present. Pain is not a severe symptom, in fact, it is more often absent than present, and when present is seldom acute; but there is more of a burning, uncomfortable feeling along the line of the colon. As the ulceration is chiefly in the colon, digestion and food absorption are little interfered with until late in the disease, or the type of disease is severe, consequently weight loss does not occur early. Loss of appetite as a result of absorption of toxic products is also a factor in the loss of weight. Fever is practically absent till late in the disease, unless subacute peritonitis or perforation occurs.

Many patients are able to keep at work for

years without much weight loss or inconvenience save for the frequent bowel passages, but the majority after a greater or less time, if the disease is constant, lose strength and are unable to work, although the hemoglabin and weight loss may not be excessive. The disease is essentially one of many months and may be of many years duration, but when the breaking comes, it is usually very quickly. In the fulminating cases the onset is rapid and within a few days or weeks the patient may be seriously ill. Diarrhaea may reach such an intensity that there is almost continuous defocation with loss of sphincter control. So much bleeding may occur that the passages give the gross appearance of pure blood. There is great loss of weight, reaching sixty or eighty pounds in a few weeks. Anemia becomes pronounced, the hemoglobin being reported as low as 15%. Severe abdominal cramps and distressing tenesmus rack the patient. Fever of a septic type is seen. Death may occur as a result of failure of the heart muscle, endocarditis, septic arthritis, perforation of ulcers or general exhaustion.

Between the extremes lie many cases which present occasional periods of marked severity followed by remissions or even latency with complete cessation of symptoms. When patients

present themselves for examination, the history usually concerns a disease of chronic character with remissions. Few are seen during the first attack. The usual history is one of recurrent attacks of "bowel trouble" apparently incited by an acute cold, sore throat, tonsillitis or bronchitis. Such patients usually consult their physicians and are apparently cured by general measures; evidently the relief of this disorder occurs during the remission stage.

II. DIAGNOSIS:

Given a history of pussy, bloody discharges one makes the diagnosis of c.w.c. by sigmoidoscopy principally and aided by roentgenography.

Dr. Buie ⁶² of the Mayo Clinic has defined for us the sigmoidoscopic picture which he has confirmed by examination of over 470 cases; and other authorities (whose experience is relatively mediocre) agree as to the value of sigmoidoscopy.

Sigmoidoscopy according to Buie ⁶² during the period of activity shows four stages:- (1) hyperemia, (2) edema, (3) miliary abscesses, and (4) miliary ulcers. A stage of remission or healing of the ulceration leaves a glazed, scarred (pitted) mucosa. The granular ulceration, the pitted scars, and contraction of the lumen of the bowel are pathognomonic.

Stage I: A diffuse hyperemia affects the mucosa of the bowel usually more marked near the anus and lower rectum; the upper limit of which it can be seen to fade out gradually into normal mucosa. When the upper limit cannot be seen with the sigmoidoscope, it can be seen in outline of the colonic roentgenograms after barium enema has been given. In Logan's series of 560 patients, 20% were involved too low to be shown by the roentgen ray, and the sigmoidoscope was the only means of making the diagnosis.

Stage II:- Edema.

The second stage manifests itself as edema or thickening of the mucus membrane. The hyperemic stage still persists. The slightest trauma produces bleeding and the mucus membrane is easily broken.

Stage III:- Miliary abscesses.

Probably the most significant phase from a diagnostic point of view is the development of miliary abscesses in the mucosa. These abscesses are not identified with the lymph follicles, but are situated diffusely throughout the diseased area. The average size of these abscesses is about

1 m.m. and they are situated immediately beneath the superficial layer of the mucus membrane.

Stage IV:- Miliary ulceration.

The abscesses rupture and leave miliary ulcers which appear as numerous yellow spots scattered over the wall of the bowel. When these spots are wiped off with a cotton swab, the bleeding bases of the ulcers appear as myriads of red spots. After this stage Buie⁶² believes that remissions are most frequent, and that, with healing, the ulcers are replaced by scars of the same size. The numerous scattered pin-head ulcers representing the active disease, associated with pock-like scars giving evidence of former activity, forms a picture which is pathognomonic and constitutes the most important single piece of evidence in diagnosing c.u.c.

Dr. Buie⁶² thinks that it is possible to determine the previous existence of c.u.c. in patients who have no symptoms of the disease at the time of the examination, by the pock-like scars which he calls the "foot prints" of previous activity.

Stage V:- Period of remission.

During these periods of activity, the infecting process extends into the mucosal and submucosal layers and there is marked

inflammatory reaction, as indicated by the extensive lymphocyte invasion. With healing, fibrosis and thickening takes place and the characteristic thickened and contracted wall of the bowel is due as much and probably more to this process than to the small petechial scars. The tube-like, narrowed, and thickened bowel wall presents the second diagnostic feature which can be seen through the sigmoidoscope and, when the disease extends high enough, gives the appearance of the straightened tube in roentgenograms of the colon. Of course this disease may be accompanied by complications and these will be discussed below under heading "Complications".

Xray findings of value in diagnosis:

Carman and Moore in a study of 600 cases have reached the following conclusions. In the early stages of c.u.c. spasm is the chief roentgenographic manifestation; this is due to irritation of an ulcerated bowel, and depending on the extent of the disease, may be localized or diffuse. In this stage of the disease the X ray studies will not differentiate c.u.c. from other forms of colitis. However, when colonic spasm after belladonna administration persists and the proctoscopist discovers

ulcers in the rectum which extend upward, the diagnosis is assured. As the disease advances and the wall of the bowel thickens, the typical roentgenographic signs appear. These consist in rapid filling of the entire bowel, marked narrowing of its lumen and loss of haustrations. Interspersed thru the bowel may be areas of contraction giving the appearance of a string of sausages. The large bowel has the appearance of a straight tube and in advanced cases may be no larger than a lead pencil. The constricted areas are due to strictures from deep ulcerations; the fact that they are constant in position, indicates that they are not due to spasm.

X ray differential diagnosis:-

The roentgenographic appearance in a well advanced case of c.u.c. is so typical that its differentiation from other lesions of the large bowel is usually not difficult.

Carcinoma and syphilis both show filling defects with abstraction and dilatation above. Syphilitic lesions of the colon are extremely rare.

Tuberculosis is most frequently found in the cecum and ascending colon; it produces irregular filling defects accompanied by alternate filling and emptying which is so characteristic.

Diverticulosis and diverticulitis both show extraluminal shadows, moreover, in the latter a definite filling defect is shown. This simulates c.a. and should never be confused with c.u.c.

Actinomycosis is localized, usually accompanied by fistulous tracts and resembles more closely c.a. or t.b. than any other form of colitis.

Lesions produced by ameba histolytica and other parasites produce no abnormal roentgenographic findings.

In certain types of chronic constipation we have a large straight colon without evidence of haustra; this, however, should not confuse as history; dilatation; and flexibility should serve to differentiate.

Differential diagnosis:

For roentgenographic differential diag., see under "X ray findings."

Cases of c.u.c. are to be differentiated from the autotoxic enterocolitis of uraemia and diabetes and other chronic conditions. The history and coexisting manifestations indicate the diagnosis. Other conditions which have to be excluded are malignancy, diverticulitis, polyposis, tuberculosis, amebic dysentery. Of these t.b. ⁶⁶ deserves the most consideration.

	T. B.	C. U. C.
1.	: early	: late
2. Loss of wt.	: gradual	: rapid
3. Lungs	: c pulmonary t.b.	: lungs negative
4. Abdomen	: slight distension	: retracted or scaphoid
5. Localization	: Cecal region first	: sigmoid and rectum
		: chiefly involved
6. Blood in stools	: absent or slight	: marked
7. X ray	: irregular, moth eaten	: colon narrow and ribbon like
8. Organism	: t.b. in stool	
9. Signiosdoscopic	: negative	: characteristic (see above)
10 Bowels	: alternating constipation	: continuous diarrhea
	: and diarrnaea or uneffected:	
11. Ileum	: often involved	: rarely involved

Although c.u.c. ⁶⁴ usually begins in the rectum it may attack any or all portions of the large bowel. Occasionally a regional ⁶⁶ or migratory type of involvement takes place and the roentgenographic appearance is so irregular that at times it is difficult to distinguish from a case of t.b. When the cecal ⁶⁵ region is involved, difficulties arise, nowever, the only real

similarity between this form of c.u.c. and t.b. is usually that the site of involvement is the same.

Amebic dysentery Microscopic ⁶⁷ examination and the finding of large numbers of endameba histolytica is more than presumptive evidence for a correct diagnosis. There are rare exceptions, such as the 5% of patients with c.u.c. who are carriers of ameba, but in most patients whose stools contain endameba histolytica intestinal symptoms are caused by them. If in addition the typical proctoscopic picture is seen, the diagnosis is established. Amebic ulcers ~~are~~ disseminated, have a punched out appearance, have a hyperemic surrounding zone of mucosa and between the ulcers will be found mucus membrane which appears fairly normal. The roentgenogram except in the more severe cases offers little help. As in the cases of t.b., the most severe involvement is on the right side; smaller defects may appear here when no trouble evidence is seen elsewhere.

Diverticulitis ⁶⁴ except in rare cases of bleeding little difficulty will be encountered in distinguishing from other conditions and here the roentgenogram will usually establish the diagnosis.

Polyposis. The history in cases of polyposis can

readily be confused with the history of a case of t.b. This is particularly true because both diseases are likely to attack young persons and because in both there is often a history of disability of long standing. Here again the proctoscope and roentgenogram will help clarify the diagnosis.

Malignant disease need only rarely present difficulties of diagnosis. The usual history of onset with rectal bleeding, relatively rapid progression, signs of obstruction in persons past middlelife, without a demonstrable t.b. focus, usually readily establishes the character of the trouble if malignancy is present.

PATHOLOGY

In chronic ulcerative colitis⁶⁷ the lesions are usually most marked in the sigmoid and rectum. Here the mucus membrane may be almost completely denuded leaving a granular bleeding surface and marked thickening and fibrosis of the wall. In other parts of the colon various stages of ulceration may be found. The mucus membrane becomes adherent to the muscular coat and loses the elasticity of motion characteristic of a normal bowel. If the inflammatory process is severe, deep ulcers going on to perforation may develop, but in this condition only a localized and not general peritonitis usually results. One of the chief characteristics is the extreme thickening of the wall of the colon with smoothing out of the folds, leaving a glazed surface. This marked thickening is first due to hyperplasia, edema and infiltration in the mucosa, and later to fibrosis in the wall. Later contraction of the fibrous tissue may result in a marked narrowing of the lumen which, if localized, may result in partial obstruction. The ileum is practically never involved. The histopathology is perhaps more variable than the gross pathology, yet it presents

merely the simple picture of acute, subacute or chronic inflammation, depending on the stage of the process. The mucus membrane and subjacent structures are usually involved. Congestion and edema may be limited to the mucosa, sub mucosa, or may involve the entire bowel wall. The mucosa may be covered with an exudate composed of pus cells bacteria and inflammatory elements. It may be devoid of glands in case necrosis has progressed. Lymphocyte and plasma cell infiltration of varying degrees may involve the mucosa on the entire colon and its peritoneal covering. There is usually marked fibrosis with thickening of the wall, but areas may be found where the wall is almost reduced to the thinness of tissue-paper. The sigmoidoscopic picture of the pathology has been discussed above under "Sigmoidoscopy". The ⁶⁸ descending colon shows numerous small round ulcers rather shallow surrounded by an edematous mucosa, the ulcers becoming deeper, longer, and more numerous toward the rectum and are best developed in the sigmoid.

ETIOLOGY

In 1928 a symposium⁶⁹ on chronic ulcerative colitis in the Haverian Society of London reported in the Lancet⁵⁰ in which such eminent men as French, Tidy, Norbury, Smith, Broadbent and Wilcox took part added nothing to our knowledge of the etiology or treatment of this disease. The participants were convinced of the infectious nature of the disease and advocated irrigations and surgical procedures in the treatment.

Chronological survey of literature.

The literature⁶⁹ on the subject of c.u.c. is briefly summarized as follows:- Wilks and Moran mentioned the disease in 1875 in their lectures on pathologic anatomy. Allchin in 1885, exhibited to the London pathological society a specimen of a colon from a case of this disease calling attention to the features which he believed distinguished the condition as a disease entity. White in 1888 gave a good pathologic description of the disease. Lockhart Mummery's first description appeared in 1907 and 1908 and at this early date he emphasized the need of proctoscopic investigation stressing the fact that knowledge before that time had been gathered chiefly from

the patients' symptoms and from post mortem examination. Allchin in 1909 wrote about the pathology. He made note of the fact that in 20 years prior to 1908, 55 patients with chronic ulcerative colitis had been admitted to Guy's Hospital, London. Hawkins in 1909 expressed the belief that "the pedigree of the disease can be traced to the bloody flux of Sydenham in 1669." Cameron and Rippmann in 1909 and 1910 reported statistics about the cases of this disease found in London Hospitals from 1888 to 1910. Jex Blake and Higge first spoke of its bacterial etiology in 1909 considering ~~as~~ factors B. Coli, Escherichia coli, B. proteus vulgaris, B. pyocyaneus and streptococci. Wallis in 1909 reported streptococci in the stools of many of these patients and emphasized the significance of oral sepsis. White in 1911 noted that he had met with cases due to B. coli and pneumococci. Hutchinson in 1911, wrote concerning treatment of the disease and commented on dietetic, medicinal, and surgical measures. Lockhart Mummery in 1911 reported on its diagnosis with the sigmoidoscope. Lindenberg in 1912 advocated surgical treatment describing colostomy as the procedure of choice. Wegele

in 1913 stressed the seriousness of rectoscopy in these cases and commented on medical and surgical treatment. Kretschmer also in the same year called attention to the exacerbations of the disease and urged surgical procedure as a last resort. Lockhart Mummery, in 1913 emphasized its serious nature by reporting a fatal case. Bassler in 1913 first suggested the significance of *B. coli* in the condition. Haskell⁵² in 1914 reported a case of acute ulcerative colitis. Albu in 1915 commented on its pathology and reported two acute and twenty-one chronic cases. Hewitt and Howard in 1915 noted its relation to polyps of the colon. Strauss in 1915 spoke of its bacterial etiology, basing his beliefs on the following facts:-

(1) In seven of his cases there was agglutination of dysentery and typhus bacilli by these serums from human beings in dilutions of 1:50 and in one case in dilutions 1:150. (2) There was the occurrence of such complications as anthraxis, iridocyclitis and venous thrombosis. Lynch⁵³ and McFarland in 1916 first described the condition in a general consideration of colonic infections.

Little appeared in the literature from then until the statistical study of 117 cases by Logan in 1919. Logan⁶⁰ expressed the belief that the basic etiologic factor was a metabolic disturbance. Lockhart Mummery, in 1920 advocated surgical treatment, suggesting appendicostomy as the operation best fitted to the needs of this condition. He also emphasized the predominance of streptococci and bacilli of the colon group in stools of these patients and the absence of parasites. Hurst⁵⁶ in 1921 expressed the belief that the condition was a post bacillary infection. Yoemaus²⁷ in 1921 found only the usual intestinal inhabitants by cultures of the stools. Leusden in 1921 wrote of the significance of colon bacilli and dysentery bacilli. Bassler, in 1922, again wrote of the significance of colon bacilli, asserting that this organism became virulent under certain conditions and ventured the designation of *Bacillus pseudo-dysentericus coli*. Rolleston, in 1923 wrote of the significance of primary injury to the mucosa of the colon brought on by dietary or other deficiencies and at the taking on of pathogenic characteristics by the normal intestinal inhabitants. Hewes in 1923, wrote of the isolation of streptococci, staphylococci, colon bacilli and gas bacilli

and emphasized the fact that often the disease appeared as a sequel to another infectious disease, such as pneumonia, influenza, measles, or diphtheria. He stated that the infectious nature of the disease is unknown. Stone¹⁹ in 1923, in advocating surgical treatment found only the usual intestinal germs. Einhorn²⁹ in 1923, in commenting on treatment, considered the dysentery bacilli as significant factors early in the disease. Brown⁵⁸ in 1923 commented on the enzymatic activity of the duodenal enzymes in cases of this disease. Logan¹⁸ in 1923 reported cure of the disease in 3 cases in which ~~the~~ of I. was administered by mouth. Strauss, Friedman and Bloch in 1924 advocated colectomy for the condition and in commenting on the etiology emphasized the predominance of strep. in washings of the colon after ileostomy. Thorlakson²⁸ in 1923 considered bacilli of dysentery as the original invaders in the disease but called attention to the fact that diplococci resembling pneumococci had been isolated in some of his cases in pure culture. He considered these as secondary invaders.

Crahn¹⁶ and Rosenberg in 1924 advocated the use of acriflavine in irrigations of the colon in the treatment of this disease, and in 1925, they stressed the importance

of sigmoidoscopy in the diagnosis. Rienhoff,²⁰ in 1925, advocated ileosigmoidostomy as a valuable form of treatment. In the same year Brown wrote of the protein etiology of the disease. Smith in 1925, described the pathology of c.u.c., and mentioned the finding of pneumococci and strept. by stool culture. Lynch and Filsen in 1925, in a report of 41 cases expressed the belief that the colon bacillus was of etiologic significance. However, they could not ascribe this note to a specific bacterium, although they were firmly convinced that there was such an infectious cause. Helmholtz in 1926 reported the occurrence of the disease in children which was the first report of its kind in the literature. Woolf in the same year emphasized that in the 35 years since White's accurate description of the disease, "The course of the disease had neither been discovered nor had much been done for the amelioration of it."

Buie in 1926 and 28th three reports described the proctoscopic picture (see above) so accurately that little doubt remained about the condition being an entity. Schur in 1927, expressed the belief that the condition was a definite entity of bacterial etiology. He based

his belief on clinical experience and a comprehensive review of the literature. Wendkos of Philadelphia, and Soper of St. Louis in 1927, reported on the use of vaccine treatment of the disease, and Chriholm, of Denver, reported the same in 1928. Bassler, in 1927, stated that the condition was an infectious disease entity but that he thought it was due to a variety of bacteria including B coli, diplost~~re~~ptococci, B~~iv~~Welchei and B. pyocyaneus. Jones in 1927 stressed the palliative effect of surgical measures on the disease. Torrey in 1927 stressed the Etiol. sig. of certain strep. and diplost~~re~~p. in the disease. Fortis in 1927, made similar observations and advocated vaccine in treatment. Alekseiev, of Russia, and Alessandri, of Italy, in 1927, spoke of the infectious nature of c.u.c. Similarly Bensarde and Oury of France, and Foukner of Germany, in the same year, reported their belief in a bacterial etiology. Dustin, in 1927, in a clinical report, considered the disease to be of an infectious nature. Brown, as late as 1927, expressed the belief that mucous, catarrhal, and c.u.c. were related conditions.

Crahn,¹⁶ in 1929 reported that organisms of the streptococcus group were obtained by culture of the

blood in two cases of severe ulcerative colitis. DeBere, in 1928, isolated diplostreptococci from the rectal lesions and by intravenous injection, he produced lesions similar to those in human beings. Garrett in 1928 observed the predominance of streptococci in culture of stools of patients c colitis. Funkhouser in the same year, made similar observations; so also did MacNaughton⁵⁹ and Santee, who stressed the probable significance of specific therapy. Horgan and Horgan (See J.A.M.A.) in July 1929 reviewed the facts of specific treatment and reported 5 cases in which the results from such treatment had been good.

The only recent article with a suggestion of other than infectious etiology is a report of 5 cases given by Larimore in 1928 before the American Gastro-Enterological Association. The patients in the 5 cases had been fed on foods presumably high in vitamins in an attempt at cure. He suggested the possibility that the syndrome was the result of a food deficiency.

Conclusion from literature survey:-

From this chronological survey of c.u.c. it becomes apparent that most men who come into contact with this

condition think of it in terms of infection, that they are uncertain of the bacterium or bacteria guilty of the invasion, that dysentery bacilli, or closely allied forms and various forms of strep., have received their share of blame, and that perhaps failure to find the specific bacteria may have been dependent on methods employed in trying to isolate them.

C. D. Murray ⁶² thinks that fear plays a part in bringing on exacerbations of the disease. Investigations of the life histories and mental attitudes of a series of 12 patients suffering from chronic ulcerative colitis revealed a close association in time between the emergence of a difficult psychologic situation and the onset of symptoms. Mental conflicts concerned with marriage were more commonly found than other types of situations which might evoke anxiety. In each case the patients ~~found~~^{met} their problems in an inadequate, infantile manner.

Lack of protective mechanism theory.

Dr. Brown ²⁵ thinks that perhaps the cause of the disease is not to be found in the presence of a definite and specific infective agent but rather in the absence

of some protective substance or mechanism, of a something which normally inhibits the bacterial invasion of the intestinal wall, perhaps due to metabolic error, or endocrine disturbance or lack of a specific bacteriophage or absence of some normal bactericidal substance in the intestinal mucosa. These ideas are purely hypotheses and are merely suggestions for research and give no conclusions or proof.

Specific theory.

Most of the studies reported thus far are reports made from observations on only a very few cases and being mostly arm chair speculation bring no or little light upon the subject. In surveying the literature, I find only one man, that of Barger of the Mayo clinic, who had done a sufficient amount of work to indicate the facts. Most observers state their conclusions from a half dozen or so cases while Barger keeps quiet till he has studied scores.

Barger⁸⁹ in 189 cases (approximately 80%) of c.u.c. in which the patients were examined at the Mayo Clinic over a period of several years, isolated a certain diplococcus in pure culture which when injected into

veins of 459 healthy rabbits gave lesions and bloody discharge from colon of 268. A report of this investigation follows:-

Report of Bargaen's Study.

Many difficulties are encountered in studying the etiology of the disease by cultures of stools. By the ordinary cultural methods, Bargaen found that bacilli of the Escherichia coli group and various supposed saprophytes overgrew any other forms. Injections into animals of strep. and other bacteria isolated from ulsters by the usual methods gave persistently negative results. It was thought that the causative organism might be sensitive to oxygen, that perhaps a medium affording a gradient of oxygen tension might serve to enhance the growth of this organism in advance of other bacteria, and that the organism of which the growth has been enhanced might localize in the colon by intravenous injection of the primary culture, just as Rosenow has found to be the case in organisms obtained from patients c other diseases. A conveniently prepared medium which furnishes these requirements is Rosenow's dextrose brain broth.

If the results obtained were carefully checked against those obtained by ordinary mediums, it was thought that perhaps the causative organism might be singled out to the exclusion of other more saprophytic forms.

The rectum was thoroughly cleaned by repeated irrigations of warm water or solution of NaCl till the fluid returned clear. A sterile proctoscope was then inserted and the surface thus exposed was thoroughly cleaned by swabbing the ulcers and applying tn. of I.

The material withdrawn was disposed of at once and in 3 ways; some was transferred to warm dextrose brain broth, some to warm physiologic salt solution, and some to slides for smears. The first was transferred to the incubator at once. The second was used for plating purposes, in shake cultures both of blood agar and of plain agar, and for streak plates on Endo's.

Dilutions varied of specimens obtained, but it was soon learned that considerable dilution was necessary if one wanted individual colonies separated for enough so that they could be picked from 15 to 18 hours later with a fine platinum wire. Smears of the 3rd specimen, stained

by Gram's method and carbol fuchsin, were examined for acid-fast bacilli and for predominating bacteria. Stools had previously been examined for endamebas and other parasites.

Diligent search for bacilli of dysentery was instituted but without success. However large numbers of gram positive diplococci were found in smears from the lesions in the bowels of patients with c.u.c. The diplococci were frequently so numerous, particularly in smears of the more acute, more severe cases, that other bacteria were not seen.

The organisms were also found in predominating numbers in primary cultures in dextrose brain broth. It was believed that growth of the causative organism might occur in this medium, since it afforded a gradient O₂ tension, whereas only the more saprophytic organisms, or those not sensitive to O₂ might develop on blood agar and in other ordinary mediums. Furthermore, localization in the colon might occur following intravenous injection of the primary mixed culture, and the causative organism might be isolated from the tissues of animals in which the lesions developed. Thus the

animal would be used virtually as an artificial culture medium for selection of the organisms that could do specific harm. Moreover if pure cultures of the organisms injected similarly after rapid subculture would produce similar lesions, such an organism could justly be considered as being a probable factor in the production of c.u.c. Positive results were obtained early in these investigations.

Healthy rabbits weighing about 2 K.G. and, free from diarrhoea, as evidenced by several days' observation were chosen. They were given greens, oats, hay and water and were observed daily. Two or more rabbits received intravenous injection of cultures from each patient. In the earlier work 2-5 c. c. of a dextrose brain broth culture containing the diplococcus in predominance was injected. Later from 3-13 c. c. of a pure, rapidly isolated culture of diplococcus was similarly injected. Rabbits that survived the inoculation were chloroformed for examination in from one to 28 days depending on the symptoms. Whether the rabbit died naturally or was chloroformed,

at necropsy culturer were taken from the blood, abdominal lymph glands and, in a few instances, from the lesions in the colon.

In smears from the lesions of patients two organisms were seen; a gram positive diplococcus and a gram-negative bacillus. In dextrose brain broth cultures made from the majority of the patients, the gram positive diplococcus grew in predominance. On Endo's medium a gram-negative bacillus grew which in all essentials was like a colon bacillus. If the tubes were heated slightly the gram-negative bacilli could be inhibited from growing entirely.

As time went on, the technic adopted for cultivating material was as follows:- Two sterile swabs were passed through the scope and, by a twisting motion some of the material from the base of the ulcer was withdrawn and transferred immediately to two tubes of warm dextrose brain broth and incubated from 4-6 hours. After from 4-6 hours one set of three additional tubes of dextrose brain broth was inoculated with material from one of the original tubes by shaking the swab into each of three tubes of sterile dextrose brain broth. A second set

were similarly inoculated with material from the other of the original tubes. One set of tubes was heated for 45 minutes at 55° c and incubated; the other set of these tubes were incubated directly without heating. In 18 hours smears were made of the growth in each of the 8 tubes, the smears were stained and examined with the purpose of selecting the tube with the largest predominance of diplococci of the variety that is to be described. Subcultures of this were made on blood agar plates. Cultures on Eado's and in dextrose broth had been made from the original swabs and were now examined. The growth here was predominantly and usually wholly of gram-negative bacilli of colon group. One set of 3 tubes was heated for 45 minutes at 55° c and incubated the other set was incubated directly without heating. In 18 hours smears were made of the growth in each of the 8 tubes of brain broth, and examined with the purpose of selecting the tube with the largest predominance of diplococci. Subcultures of this were made on blood agar plates. Cultures on Endo's medium and in dextrose broth had been made from the original swabs and were now examined. The growth here was

predominantly and usually wholly of gram-negative bacilli; which by further study were found to belong to the colon group.

The subculture of the first blood-agar plate was made by mixing one drop of inoculated dextrose brain broth with 10 c. c. of physiological salt solution and one drop of this mixture in 10 c. c. blood-agar. These plates were incubated over night.

The following morning colonies of diplococci were surrounded by a green zone, with a faintly hemolytic zone between the colony and the green zone. The colonies were picked with a platinum wire and transferred to fresh tubes of dextrose brain broth and incubated 18 hours.

The organism so isolated has the following characteristics:- It is lancet-shaped, slightly larger than a pneumococcus, gram⁺ and from early subculture never appears in smears in groups of over two or four. The appearance of its colony on mannite is typical, so also is that on mannite agar, where it appears as a fine translucent colony in striking contrast to the so-called enterococcus of Houston and McCloy, which grows as a large white opalescent colony. The colony of strep.

fecalis appears much like that of the enterococcus. The diplococcus and enterococcus do not usually ferment mannite; Strep. fecali does. The diplococcus does not ferment inulin; the diplococcus pneumonia does. The diplococcus ferments dextrose, lactose, saccharose, maltose, raffinose and salian. Significant differences between the enterococcus and the diplococcus are these:- The diplococcus does not grow on plain agar, or only after repeated subculture and then only sparingly; it does not grow on gelatin, and it does not coagulate milk.

To classify the organism of c.u.c. one must take into consideration its tendency to form chains, after repeated subcultures, its lack of power to ferment inulin, its green zone on blood agar, and its tendency to localize in tissues after intravenous inoculation, like other strep. It probably belongs to the strep. group ~~and the viridans species.~~

With this organism, rabbits have been immunized to produce a diagnostic serum. The diplococcus was grown in 100 c.c. of 2% dextrose broth for 24 hours. The broth culture was centrifuged, the supernatant fluid was suspended in 100 c. c. of physiologic salt solution. This was preserved at ice box temperature. .5 of a c.c.

of this suspension in solution of NaCl was injected intravenously into a large rabbit, every two days another injection was made and the amount was increased .5 c. c. each time. The agglutination of the diplococcus in suspension of physiologic solution usually occurred in adilution well above 1:1000. Horses were also immunized by methods of Rosenow.

In many of the rabbits given intravenous injections with the larger doses of the primary culture in dextrose brain broth, in which diplococci were the vastly predominating bacteria or with the pure cultures made by rapid subculture of the original culture, severe diarrhoea developed in from 24 hours to several days after the injections. Often there was blood and mucus in the stools. The rabbits lost weight and wasted rapidly.

In 189 cases (approximately 80%) of c.u.c. in which patients were examined at the Mayo Clinic over a period of several years, the diplococcus was isolated in pure culture. With these strains, 459 healthy rabbits were given injections. Evidence of disease of the large intestine, from marked diarrhoea with few if any nemorrhages, to extensive hemorrhages and severe ulceration with bloody discharges from the rectum developed

in 263 rabbits. The seat of election of these lesions corresponded rather accurately to that in the patients. Lesions as a rule were more extensive near the rectum and often involved only the distal half of the colon.

In a few instances, lesions occurred in other parts of the g.i. tract in the form of submucous and disseminated hemorrhages. Rarely were lesions found in any other organs of the body.

Similar cultures were made in 98 consecutive control cases in which proctoscopic examinations were made and in which the mucosa of the bowel was normal. Diplococci in some essentials like those found in cases of c.u.c. were isolated from 16 cases. Six of these strains were agglutinated by the immune horse serum; only 4 produced lesions in animals. These lesions were in the form of a few minute, disseminated hemorrhages into the colon. Other strains of strep. were frequently isolated. None produced lesions in rabbits similar to those described.

Rosenow, Nickel, Meisser, Cook and others working along similar lines with similar cultural methods in conditions other than c.u.c. with other strains of strep.

in the same laboratory during the same period, with animals from the same common stock, induced lesions in the colon only in rare instances (not more than 2%).

In 31 of 35 dogs which were given injections in a similar manner to that used in rabbits, with from 3-615 c.c. of a dextrose brain broth culture of the diplococcus even more striking and more characteristic lesions of the colon occurred. In several dogs, bloody diarrhoea was so severe that rectal prolapse occurred, providing ample opportunity to observe with the naked eye lesions like those seen with the proctoscope in human beings. Several other dogs were examined proctoscopically and the typical lesions observed.

An organism in all essentials like the diplococcus described was isolated by blood culture from 6 patients with severe fulminating, acute c.u.c. All of these patients were acutely ill with a high septic type of fever, marked abdominal tenderness and extensive involvement of the colon. Three of the six patients died, and in two the organism was isolated at necropsy from the hearts blood. In sections through the lesions in the colon in these cases and in sections through the ulcers

in the colons of 12 other patients who died from c.u.c., large numbers of diplococci morphologically like those described were demonstrated in the depths of the inflammatory and granulation tissue.

Another seemingly significant factor bearing on the causative relation of bacteria to this disease is the clinical observation that frequently tonsillectomy, removal of infected teeth, or acute infections of the upper respiratory tract, cause marked acute temporary exacerbations of the disease. This suggests the presence of the causative bacteria in these foci.

Diplostreptococi, in all essentials like those isolated from the rectal lesions, have been isolated from periapical abscesses of teeth or from buried tonsillar abscesses, and cultures of these when injected intravenously have produced lesions in animals like those described. These organisms were agglutinated by the immune rabbit and horse serums. This has been the experience with the use of strains from many patients on several hundred rabbits.

Cook working with Rosenow has induced periapical infections at the apices of teeth of a series of dogs

by removing the pulp and inoculating the pulp canals with dense suspensions of diplococci isolated from the blood and mesenteric lymph nodes of rabbits in which hemorrhagic colitis developed following the intravenous injection of diplococci which in turn had been isolated from the lesions or foci of patients with c.u.c. From 3 to 12 months later c.u.c. developed in a number of these dogs and was demonstrated proctoscopically and at necropsy.

Bargen ²¹ states that the organism sometimes localizes in the g.b. of rabbits. 18 rabbits were fed on vitamin-free food for 2 weeks to reduce their resistance. At the end of this time 9 were injected intravenously with 5 c.c. of a dextrose brain broth culture of the freshly isolated diplococcus. All were dead within 5 days; 3 had empyema of the gall bladder from which a pure culture of the diplococcus was isolated.

Of the other 9, 5 died apparently from starvation with certain symptoms of a deficiency syndrome while 4 lived 2 months on the diet.

The culture of the diplococcus isolated from these gall bladders were injected intravenously into 2 young dogs. Repeated daily injections were given in 12,

20, 20, 20, 20, and 30 c.c. in an effort to produce a chronic disease more like that in human beings, since the lesions in rabbits were rather of the acute fulminating type. On the 4th day the dogs began passing bloody mucus; on the 6th there was marked rectal prolapse exposing an edematous, granular, easily bleeding, superficially ulcerated mucosa, the typical picture of early c.u.c. At the end of 2 weeks one of the dogs began to improve, and repeated large doses of the organism had no effect. When it was killed at the end of 3 weeks, a healing ulcerative colitis of the lower 6 inches of the colon was found. In the other dog, colon changes were demonstrable by roentgenray with barium enema at the end of 3 weeks, after which he began to get well. The possibility that the g.b. might act as a focus for harboring these diplococci made it reasonable that other distant foci in human beings might be of importance.

Garvin ⁷² states that by many observers it has been

noted that symptoms have often been ushered in by an acute upper respiratory infection, or soon after some dental infection. Not infrequently patients with c.u.c. have exhibited repeated severe bowel reactions following extraction of infected teeth and tonsils and it has been further observed that the removal of such foci often caused remarkable improvement.

Substantiating Bargaen's Work:

Kracke reports isolation of the diplococci from stools in 10 cases showing pus and blood in discharges and this organism when injected into rabbits (fed on vitamin diet to lower their resistance) gave evidence of c.u.c. He could not grow the diplococci from normal stools.

Fradkin and Gray³⁴ have carried out work with patients with c.u.c. and substantiate his findings. During the past 2 years (1928-30) they had under control 15 patients with a definite history symptoms and proctoscopic evidence of c.u.c. These patients varied in age from 18 to 35 years, one being 42. In all these patients, symptoms had been present for from two months to four years. Of the 15 patients, three

failed to show the Bergen diplococcus after repeated bacteriologic study. In the remaining 12 the organism was found after the first, second or third sigmoidoscopic examination. The organisms isolated from the patient's colon were in each case agglutinated by the patient's serum in dilutions of from 1:20 to 1:60 but were never agglutinated by control serum. Four rabbits were injected intravenously with 5-10 c.c. of a pure culture of the diplococcus. A total of about 40 to 50 c.c. was given to each during a period of from 5 to 7 days. Two of the rabbits developed severe arthritis, completely disabling them in locomotion. Two rabbits developed a diarrhoea with quite an extensive proctitis. A direct rectal smear showed the same diplococcus. These two animals died at the end of the fourth day. Post mortem examination revealed lesions in the large intestine similar to those found in the early stages of non specific ulcerative colitis in man, such as pinhead ulcerations. Microscopic sections of the intestine showed marked congestion, small hemorrhages, edema, ulcerations, and hyperplasia of the lymph follicles. A bacterial stain of the tissues showed myriads of the diplococci in

the submucosa of the intestine. The diplococcus was recovered in pure culture on post mortem from the heart's blood of the rabbit ~~from the bite in the g.b.~~, and on direct smear from the mucosa of the intestine.

Perhaps produced by a group of organisms.

Streicher and Kaplan ⁴⁷ in a study of 65 cases 1926-9, found in most cases of ulcerative colitis green-producing gram positive diplococci are found predominating which by reactions on different sugars included 57 different strains. In 5 cases strep. hemolyticus was isolated and symptoms persisted after vaccine therapy; whereas in 52 cases without strep. hemolyticus, symptomatic cure occurred. In no normal case were they able to isolate hemolytic strep. Rabbits which were inoculated with hemolytic strep showed lesions similar to those produced by the green diplococci. The animals lived from 28 days to 5 months. On autopsy the majority of animals showed severe congestion of the blood vessels, marked hyperemia and edema of the colonic mucosa. In one autopsy the green diplococci were isolated from ulcers of the colon of the rabbit. Of the 3 rabbits inoculated intravenously

with the pure culture of hemolytic strep, the autopsy of one showed congestion, hyperemia and edema while that of the others showed ulcers of the colon from which hemolytic strep were related. They think that evidence for non specific infectious nature of c.u.c. is also evidenced by the fact that cases of ulcerative colitis in which injections are made with the vaccine from a pure culture of a green diplococcus show little or no progress, whereas the same cases treated with a polyvalent autogenous vaccine give encouraging results.

Dr. Paulson also thinks that there may be a group of organisms concerned. Fourteen cases of acute exacerbations of c.u.c. were studied with reference to a bacterial etiology. Ten distinct types of strep. were isolated in these cases. No one type was present in more than three cases. Seven types of these strep. were intravenously injected into 34 rabbits, five of which produced lesions in these animals. Of 30 that come to autopsy, 14 showed lesions primarily in colon and rectum. He thinks the gram positive flora in cases of ulcerative colitis is due to hypermatibility of large

bowel which thus might account for presence of ileal flora in the affected parts of the colon where blood, mucus and pus might result in a multiplication of the large numbers of cocci brought down from the ileum. Normally the ileal flora is predominantly gram ~~+~~ while colonic flora is gram negative.

Not non-specific foreign protein therapy.

Many physicians believe that the autogenous vaccine has the properties of non-specific protein therapy. That this is not true ⁴⁷ is clearly demonstrated by the fact that negative results are obtained when typhoid vaccine or milk injections are substituted in these cases.

TREATMENT

There ⁴³ have been about as many types treatment for c.u.c. as there have been contributions to the literature on the subject. This is in contrast to the generally accepted and fairly well standardized treatment of peptic ulcer. C. u. c. while not as common as peptic ulcer, is undoubtedly more serious and demands standardization of treatment.

In the main, physicians interested in the treatment of c.u.c. have been divided into 3 groups: (1) those who believed it was an infectious process; (2) those who believed it was metabolic in origin; and (3) those who believed it was a surgical problem.

Those who believed in the infectious theory have advocated irrigations and instillations. Among the favored drugs for irrigations were argyral, silver nitrate, tannic acid, boric acid, sodium chloride, potassium permanganate, and more recently mercurochrome, acriflavin and gentian violet.

There are a few general conditions ⁴² to be borne in mind in any treatment. We are dealing with an

infectious process and in some cases a debilitated patient. The gut is inflamed and ulcerated and in this condition needs rest and protection. Treatment consists in building up the general health of the patient, combatting the infection, and healing the ulcers. It must be remembered that there is a tendency to remission and that perhaps this natural tendency is the cause of the results claimed for fantastic diets, etc. Irrigations have been given as copious colonic douches, as through and through drainage with appendicostomy or cecostomy, and by the Einhorn tube²⁹ which consists of flushing the intestine by a tube passing from mouth to large bowel.

Advocates of the metabolic and deficiency theory found support in the fact that liberal feeding of articles of food of which patients had been deprived resulted in improvement; mental hygiene and sun-baths resulted in marked systemic improvement. Furthermore, the administration of certain drugs, particularly iodine, brought about remission. 18

Cecostomy, appendicostomy, ileostomy, colectomy, ileosigmoidostomy, and various rectal operations have

been performed for c.u.c. Ileostomy effected complete short circuiting of the fecal stream; appendicostomy and cecostomy accomplished chiefly an ostium for irrigations. Colectomy, with enormous associated risk, removed the major part of the diseased tissue. Ileosigmoidostomy, also with considerable risk, accomplished a part of what ileostomy did without the disadvantages.

MEDICAL TREATMENT

Tidy ³⁶ states that direct applications to the bowel are the basis of treatment.

Warmth. It is essential that the patient should be kept warm in order to diminish loss of heat from the body.

Fluids. Must be given in considerable amounts to repair the loss from the body. One or two ounces may be given every 20 to 30 minutes between meals.

Diet: It is of the greatest importance that the patient should get sufficient nourishment. Nourishing general small residue diet is indicated with high vitamin content.

Starch and Opium enema.

When the patient first comes under observation treatment ³⁶ should commence with starch and opium enemata. ($\frac{1}{2}$ $\bar{3}$ starch 20 $\bar{3}$ water. 2-4 $\bar{3}$ injected, 20-40 min. tn. of opium at a dose.) It should first be given at night in order to obtain rest and sleep. It should not be given on more than 3 days consecutively, or more than 5 x a week. A few evening injections will reduce the number of night stools. After an interval of

a day, two or three injections are given in the mornings in order to reduce the number by day. Subsequent treatment often involves giving alternate morning and evening series of two or three injections.

Colonic washes. When the stools are reduced by half, colonic washes are begun. Many patients cannot stand more than three washings a week. (NaCl 1 10 using 2.0.) If the stools become more frequent one should return to the starch and opium enemata.

Medicated enema. When the stools are consistently less than 5 per day, the patient is ready for medicated enema. If medicated enemas are started before the intestine is in a fit state the pain will be too great to permit retention, and may increase the stools.

Tidy advises Alborgin 35 gr. in 30 ounces of normal saline.

After ³⁶ 6 medicated enemas it is advisable to return to colonic washes for 2-3 weeks and then repeat for 2-3 months.

Surgery according to Tidy is only indicated in cases of incontinence of feces.

Drugs:

Morphine Tidy thinks ³⁶ should never be given by injection as the patient likes the comfort it gives and will resist any form of active treatment. A maximum ³⁶ of 5 gr. of tn. of opium may be given 4 times a day.

Drugs by mouth apart from morphine have very little effect during the acute stages. In the later periods of improvement certain preparations are of benefit. Mistura creta, bismuthsalicylate, and avamatic sulphuric acid are the most valuable.

Charcoal and Kaolin may have a place in the treatment.

Instillations.

Bassler ³ uses (1) nightly instillation of 4 ounces of following:

Iodoform	8.
Bi subnitrate	120.
Olive oil	1000.

(2) Coats gut every other days half and half mixture of calomel and bismuth nitrate powder.

Fansler as treatment by drugs is more or less of a hit or miss proposition, and it is hard to tell just what drug will act best in any particular case. In cases with marked diarrhoea opium⁴² will control the pain and diarrhoea. Tannigen and bismuth subcarbonate are also useful for this. Tannigen, grains 5 every 2 hours or bismuth subcarb. in teaspoonful doses every 2 hours may be used. Kaolin and borium sulphate are also recommended in very large doses but should not be given in acute stage as they act as mechanical cleanser and absorbent. Three or four ounces of either of these drugs cause the gut to appear cleaner and the ulcers more healthy.⁴² Since production of the ulcers and lack of irritation are desirable, Fansler⁴² believes that bismuth subcarbonate in liquid petrolatum is a desirable mode of administration.

Various dyes by mouth have been advised. Fansler⁴² states he has used them all, gentian violet, mercurochrome, and acriflavine but cannot state their value.

Surgical Treatment.

Lockhart Mummery⁴⁰ state that surgery appendicostomy or ileostomy are indicated and quote figures:-

Out of 83 cases

33 medically treated gave 78% mortality.

49 operated " 18% "

However the majority of observers in this country advise surgery only in fulminating cases.

Ileostomy.

Stone ⁷ thinks that there is a definite and important place for surgery in the handling of the disease. Three classes of cases may require operative treatment: the relatively mild group that fail to improve in spite of medical methods and results in chronic invalidism, the persistently recurring cases, and the fulminant cases with great loss of weight, deep anemia and ~~asthenia~~; and he thinks ileostomy is the operation of choice.

Ileosigmoidostomy.

Reinhoff ²⁰ having relieved 2 patients by ileosigmoidostomy, advises that operation because he thinks it gives complete rest to colon without ileostomy and the diseased bowel more nearly approximates the normal than often other forms of surgery. He advises a preliminary colostomy above the sigmoid to prepare the

sigmoid and rectum for an anastomosis with a ileum thus giving a new disease-free tract.

Ileostomy

Fansler⁴² thinks that unless medical measures fail surgery is not justified; and in such cases he advises ileostomy.

Soper⁴¹ thinks ileostomy should be postponed till all methods of treatment have failed.

Fansler⁴² thinks that low residue diets should be given. As the disease subsides and the colon dilates to its normal size a certain amount of residue is advisable. He thinks that a well balanced diet is essential. In any infectious process it is necessary to keep the strength at highest possible level, and this is not done by a freak diet lacking half of its vital elements. Any diet should contain ample amounts of calcium and vitamins A, B, C, and D. In addition to the regular diet the patient should be given orange juice, tomato juice, cream, and calcium lactate. Fansler⁴² thinks that in cases in which bleeding is pronounced, calcium checks it and hastens healing.

High vitamin. In treating 5 cases Larimore³² found that

with the addition of high vitamin content to dietary the cases began to promptly improve. The healing reaction of the membrane was prompt.

Sachs⁷² has followed Larimore's diet of high vitamins and in 3 patients good results were effected.

Local medicated enema

Hargis⁷⁴ in cases in which he has tried everything he could think of with no effect, has obtained cures in a few days by pouring more than $\frac{1}{2}$ ounce of pure pine tar into the rectum.

VACCINE TREATMENTBargen's idea of the treatment:

I shall present the Mayo Clinic's plan of treatment which is consistent with their acceptance of Dr. Bargen's discovery of etiological agent (see above.)

Experimental and clinical evidence ⁴³ suggests that distant foci of infection are related to the disease in the colon. Attempts are first made to immunize the patient against the diplococcus by the subcutaneous administration of the vaccine and filtrate. The second part of the treatment is the eradication of foci.

The diet should be liberal and patients allowed all good wholesome foods with a minimum of roughage.

In a certain number of cases other supportive measures are necessary. Kaolin and bismuth have proved valuable adjuncts in the treatment. Opium may be administered to relieve pain; hot abdominal stupes occasionally afford relief. The administration of tñ. of iodine by mouth ¹⁸ has definitely produced remissions selected cases. Of the analine dyes, gentian violet offers considerable promise and its administration is

rational in as much as in rather low dilutions it kills the diplococcus in the test tube. Recently in the Mayo Clinic gentian violet has been administered by mouth in both the liquid and tablet form.

Bargen thinks little of colonic irrigations as they have found that the cases are exceptional in which colonic irrigation are helpful when simpler means are of no benefit. If only the rectum and sigmoid are affected and ulceration is extensive, local applications of witch-hazel, mercurochrome, sodium-chloride, gentian violet and argynol have definite value; however, this group represents only about a 1/5 of the cases.

The usual anaemia treatment is indicated.

Operative measures were rarely necessary; however there are a few patients whose reserve is so depleted that they will not respond to medical treatment.

Vaccine and Serum:

In severe, fulminating cases Bargen¹³ thinks passive immunization is desirable. In 7 cases of acute fulminating ulcerative colitis, serum from immunized horses was given intramuscularly in repeated daily increasing doses over a period of 3-6 days. Two patients

were made clinically well and have remained so for seven and twelve months, respectively. The other five patients were permanently improved, the fever subsided, the blood in the stool stopped, and movements reduced to a minimum but none were entirely relieved from symptoms. A few years ago ileostomy was performed in such cases with a high mortality rate as the result. In at least 6 of the seven cases ileostomy was not necessary because the serum was used. With the use of vaccine and serum, ileostomy has become limited to a few advanced cases in which reserve has apparently been so depleted and in which there is so much destruction of tissue that antibodies cannot develop apace with infection and to cases with complications such as malignancy, stricture, perforation.

Soper isolated Barger's diplococcus in 18 cases of c.u.c. and thinks it is the primary etiologic agent. He tried autogenous vaccine therapy but was disappointed with the results.

Vaccine treatment is or is not foreign protein therapy.

No. Many physicians believe that the autogenous vaccine has properties of non specific foreign protein therapy.

This is disproven ⁴⁷ by the fact that results are lacking when milk or typhoid vaccine are used.

Yes. Fansler ⁴² thinks that in his cases, the giving of casein routinely into the muscles has shortened the course and hastened healing. In Germany milk injections have been used and antidysenteric serum in England has given results in some cases. These things indicate to him that the benefit is due to foreign proteid reaction.

L. A. Buie ⁴⁷ agrees with the principles of treatment outlined by Bergen and includes:-

- a. Erodicare foci.
- b. Special diet and supportive measures.
high vitamin; high calorie; little residue.
- c. Specific vaccine.
- d. Local medication to cure secondary infective
type folces
- e. Ileostomy only as a life saving measure.

Substantiating Bergen:

In reporting two cases which responded poorly to general measures, Wendkos found that Bergen's vaccine gave apparent cure.

Rehuss ³³ states that he has repeatedly isolated

an organism that acts similar to Bargen's bacteria. He states that in his experience he feels the vaccine therapy has been of value although I find no literature reports of his results.

Polyvalent vaccine.

Streicher ⁴⁷ thinks that the disease is caused by a group of bacteria and hence advocates polyvaccine. In cases of ulcerative colitis in which injections were made with the vaccine from a pure culture of a green diplococcus shows little progress, whereas the same cases treated with poly valent autogenous vaccine gave encouraging results. 80% showed remarkable improvement. Non irrigations or instillations were employed. Only other treatment included rest, relief from mental strain, eradication of foci, high vitamin, high calorie, low residue diet.

If we assume ⁴⁷ that the autogenous vaccine therapy is specific or is actively immunizing the patients, we should not expect symptoms to recur. In a series of 65 ⁴⁷ patients 80% showed no remission for over 2½ years.

PROGNOSIS

All authorities agree that recurrences are common to c.u.c. I have not been able to find any statistics as to the frequency of recurrence or any data regarding effect of treatment on recurrences. Streicher ⁴⁷ is of the opinion that recurrences are less frequent 80% of 65 cases after vaccine treatment not showing recurrence for over 2½ years.

Fansler ⁴² sums up the situation by stating that the prognosis is always uncertain. There are a definite number of permanent cures. Owing to the fact that recurrences sometimes occur several years after an apparent cure it is almost impossible to come to any conclusion as to the actual percentage of cases in which there is no recurrence after the first attack. In many cases in which all traces of the disease do not disappear, the patient may be apparently in good health and be able to attend to his usual duties. In cases in which the colon is involved diarrhoea is more or less pronounced and the general health suffers.

In 1919 at Mayo Clinic before use of vaccine therapy, Logan reported the prognosis as serious. There

were a few cures but mortality was high, 7.5% of 66 patients who stayed at the clinic under medical care but a short time, and 27% in those that underwent operation (13 cases) of whom 5 were listed as in poor condition, 8 in fair condition and 1 in good condition.

It is difficult to comment on "Cure" of ulcerative colitis. One thinks more of control of the disease, but by virtue of the fact that the numbers of controlled cases treated by Barger's method increases annually and that some have gone as long as 5 years without a return of symptoms, it seems as if the present form of treatment offers a hopeful outlet for future therapeutic endeavors.

COMPLICATIONS

Polyposis

Bargen¹⁶ in a summary of 693 cases of c.u.c. found polyposis in 10%. It occurs after severe colitis or in long-standing, slowly progressing colitis in which there is a tendency to recurrent severe exacerbations of the disease. The polyps contain large amounts of inflammatory tissue. Proctoscopic examination is the best means of diagnosis although roentgen. examination gives information in many cases. Bargen¹⁶ has seen patients in severe exacerbations of c.u.c. with formation of polyps later and finally malignant disease.

Malignancy

Struthers emphasized the relationship of c.u.c. and polyposis and suggested that malignant disease may follow. Hewett and Howard made similar observation. In view of the various reports in the literature, the frequency with which polyposis has occurred in the series of cases of c.u.c. at the Mayo Clinic and the simultaneous occurrence of polyps and carcinoma in the diseased bowel, Bargen¹⁰ offers the following hypothesis: the sequence of events in some cases of malignant disease

of the colon is c.u.c.; multiple polyposis and malignant disease.

Ocular lesions

Sometimes ocular lesions occur with c.u.c. Crahn¹⁶ thinks that this is due to habit of some therapeutists of limiting the diet of patients leading to a vitaminosis. It would appear possible that all forms of conjunctivitis and keratitis described in this disease are of the same nutritional nature, namely, that of an avitaminosis, non-bacterial in origin, clearing up or improving promptly upon the administration of a generous and general dietary.

Bargen in a series of 693 cases seen at Mayo Clinic
1923-1928, summarizes the complications of c.u.c. as
follows:

<u>Complication</u>	<u>Cases</u>	<u>%</u>
Polyposis	69	10.
Stricture	59	8.5
Arthritis	30.	4.3
Perirectal abscess	26	3.7
Skin lesions	17	2.45
Renal Insuff.	8	1.15
Endocarditis	7	1.
Splenomegaly	7	1.
Perforation	18	2.6
Malignant disease	15	2.16
Ocular disease	5	.7
Hemorrhage (fatal)	3	.4
Renal calculi	2	.2
Mesenteric thrombosis	1	.15
Tetany	1	.15

SUMMARY

1. Diagnosis

C.U.C. is characterized by bloody, pussy stools and may be diagnosed by proctoscopy and roentgenologic study.

a. Proctoscopy shows a picture characteristic of no other condition; namely, miliary abscesses, miliary ulcers, and glazed, pitted (pock-like) scars.

b. Roentgenologic study shows loss of haustra. and small lumen (with atropine) giving lead-pipe picture of lower part of colon. Localized constrictions may give string of sausages appearance.

2. Etiology

a. The disease is conceded to be infectious.

b. Bargen, thru immense experimental work, has rather definite proof that a specific diplococcus is the cause; and is backed up by several other workers.

c. Some think a group of strep. is the cause.

d. The disease may arise from definite foci of infection.

3. Treatment

a. Numerous drugs, instillations, and irrigations, have been advised but none are outstanding.

b. At Mayo Clinic the following treatment is recommended with good results in several hundred cases:

1. Eradicate foci of infection.
2. Special diet and supportive measures, high vitamin; high calorie; little residue.
3. Specific vaccine prepared from Bargen's organism.
4. Serum from horse immunized to the diplococci.
5. Local medication to cure secondary infective type of ulcer.
6. Ileosigmoidostomy only as a life-saving measure.

c. Surgery, ^{to} ileosomy, or ileosigmoidostomy, are not advisable except in unresponsive medical cases.

4. Prognosis:

As recurrences are common, it is difficult to speak of cures.

- a. Operative treatment gives higher mortality than medicinal.
- b. "Specific" vaccine treatment gives less recurrences.
- c. Disease is serious and many die after several recurrences.

5. Complications:

- a. Complications are both local and general.

- b. Polyposis, stricture, and arthritis are the most common complications.
- c. Polyposis may lead to malignancy.

Conclusions:

Chronic ulcerative colitis may be diagnosed by the proctoscope and by x ray study, often by the former alone. Barger has discovered the cause of c.u.c., namely, a certain diplococcus. Treatment is best carried out by vaccine therapy, using cultures of Barger's diplococcus; and, an immunized horse serum in fulminating cases. As foci of infection often are the incubators for the bug, I think removal of these areas is advisable.

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