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CHRONIC ULCERATIVE COLITIS

A senior thesis
prepared and written by
Jacob O. Mall
April 1931.

[Handwritten note: Inaccurate statement. This only for some quotations. Assuming credit as his own. Continues too brief.]
THE ETIOLOGY OF ULCERATIVE COLITIS

The colon is one of the most important organs of the body both in health and disease, and is perhaps the most important organ of the gastro-intestinal tract. More diseases can be traced to the colon either as a direct cause or a condition maintaining the trouble, than all the other organs combined. Before considering the etiological factor of ulcerative colitis, I believe it well to consider a little anatomy, physiology and pathology of this organ, calling particular attention to those points which have made for the many theories since the earliest description of this condition by White (1), who in 1888 reported eight cases of this condition, is regarded as the first to have adequately described its pathology and symptomatology, and only since has this condition been considered as a distinct entity. The earliest monograph on this subject was written by Gemmel (2) in 1898. Bargen (3) states that previous to the sigmoidoscope the condition was diagnosed only at necropsy.

Ulcerative colitis is a treacherous disease it may be either chronic or acute and is considered as non-specific. Chronic ulcerative colitis is characterized by a chronic inflammation of the mucous membrane and walls of the large intestine, in the pathologic picture of which ulcerations predominate. The ulceration usually begins in the rectum and spreads upwards eventually to involve the entire colon. It may, however, affect any one part, or several separated parts of the tube. The course
is in most cases a chronic one, extending over months and years, but the symptoms are usually not continuous during this malady. The symptoms are fever, malaise, prostration, protracted and persistent diarrhea with some tenesmus, and the passage of blood, mucus, and pus. Distress from gas, and grunting and other sensations along the course of the colon, are often experienced. Much weight is lost, a peculiar grey pallor is common, and varying degrees of anemia exist. In the very severe cases, the body has a peculiar odor and the face a hopeless expression.

Ulcerative conditions of the colon may have the following etiological bases: (a) Constitutional diseases, such as Bright's disease, gout, lead poisoning and cardiac disease; (b) specific bacterial or protozoal diseases, such as typhoid, pneumonia, amebic dysentery, bacillary dysentery, tuberculosis and syphilis; (c) Malignant disease; (d) trophic disturbances due to interference with the nerve supply of the colon; (e) mechanical trauma, such as hardened feces, foreign bodies, etc., and (f) vascular changes, such as embolism of the mesenteric arteries and cirrhosis of the liver. I shall not discuss ulcerative conditions of the colon due to these etiological factors.

As to general prevalence of ulcerative colitis; this condition is restricted neither to season, locality nor zone. It is an involvement which is found universally. In recent years, especially since the Great War, it appears that the non-specific ulcerative colitis is becoming more prevalent. It is not believed that improvement in diagnostic acumen and methods, or even erroneous diagnoses, can be held responsible wholly for this in-
crease. It has no respect for age or sex. Bargen's reports show that the cases appear to be equally divided among both sexes. The greatest number of cases reported fall within the third, fourth, and fifth decades of life. Geoffrey Bourne (4) has collected from literature up until 1926, ten unquestioned cases in children whose age ranged from 7 to 15 years.

The development of the final stage of chronic ulcerative colitis passes through three characteristic stages: Stage 1. A diffuse hyperemia of the mucosa of the rectum and sigmoid: Stage 2. Edema or thickening of the mucous membrane. The hyperemia persists. At this stage the slightest injury causes bleeding. Stage 3. The most significant phase is the development of miliary abscesses. These are scattered diffusely throughout the diseased area. The abscesses are about 1 mm. in diameter. In stage 4, the abscesses rupture and leave miliary ulcers which appear as numerous yellow spots on the walls of the bowel. When these yellow spots are wiped off the red, bleeding base of the ulcer is left. This is the stage at which remissions are common. The numerous scattered, pinhead ulcers representing the active disease, associated with pocket-like scars giving evidence of former activity, form a picture which is characteristic of ulcerative colitis. If condition is severe, deep ulcers, going on to perforation, develop. Small round cell infiltration of the submucosa and muscular layers is very marked. According to Mc-Millan (5) and Kantor (6) there is an extreme thickening of the wall of the colon and smoothing out of the folds (as demonstrated by X-ray) of the mucosa, leaving a smooth, glazed surface. Thickening is caused early by hyperplasia in the mucosa and,
later by the fibrosis which develops in the deeper layers. After some time the contraction of this fibrous tissue results in a marked narrowing of the lumen of the bowel which is permanent and, if localized, may result in a partial bowel obstruction.

The small intestine is the principal site of digestion and absorption as has been proven by more recent research, but in earlier times the stomach and colon were thought to have most of these two functions. The reason for this was that early experimentalist discovered that feeding could take place through the rectum before they really had done any experimental work on the small intestine. The fact that some absorption takes place in the stomach was well borne out by certain drugs which show their effects before they could be expected to have passed into the small intestine, led to numerous ideas which since have been disproven. The food is practically as much liquid in condition when it leaves the small intestine as when it enters it. Therefore we must consider what happens when it passes through the ileo-cecal valve.

It immediately strikes reversed peristalsis, is checked in it's onward course and is slowly churned back and forth in the cecum and ascending colon for approximately twelve hours. Here, it is estimated after all the digestive juices have been added and all the ferments and normally found bacteria to digestion are there, is where the remainder of digestion takes place. Nicklas (7) regarded the chief functions of the colon to be absorption which has not taken place in the small intestine and of water from the liquid masses coming from the ileo-cecal valve, elimination of
organic debris and production of mucus. At the mid-point, so-called Cannon's valve, which is not a valve but a narrowing of the colon which is a point where embryologically the hind gut and the fore gut joined, is the first point where we commence to notice from in the fecal material, showing that real absorption has taken place. Gradual absorption is increased as the fecal material is passed from pouch to pouch until finally the food arrives at the sigmoid flexure where all the liquid is removed except sufficient to keep the material in proper consistency for expulsion.

Klothe (8) states that the recent physiological studies have shown that the mucosa reacts to mechanical and chemical stimuli in the same sense as the muscular coat. The plastic of the mucosa is conditioned by the muscularis mucosa innervated by the autonomous nervous system. The stimulus originates from Meissner's plexus and the ganglia of the muscularis mucosa. Forssel speaks of an autoplastic of the mucosa. He ascribes to the muscularis mucosa the coarse work of the gastro-intestinal movements, which he ascribes to the mucosa of the fine regulation of the chemical work. Although the configuration of the mucosa varies with the individual, there are certain limits which can be considered as normal. The inner architecture of the mucosa shows a multitude of transverse and longitudinal folds frequently spiral-shaped crossed figures with soft transitional folds. Normally we find as a rule delicate fine lines; sharp edges and margins are completely absent. It is reasonable to assume that functional disturbances, such as we designate by mucous colics,
must present a different picture of the mucosa. Macroscopically we are unable to find any pathology in this condition; histologically we find as a rule a slight increase of the round cells between the tubular glands, which is usually considered as a slight degree of secondary inflammation. In all cases designated clinically as colica mucosae we have obtained a picture which can be considered as the result of hyperirritation. In one of our cases we had to deal with an unhappily married woman 26 years of age, who besides other nervous disturbances, also suffered from attacks of colica, occurring at regular time intervals, and associated with a discharge of mucus. There was found here an increase in the number of folds, in some places the folds are spiral shaped; the picture also revealed a number of particles of mucus. This type of picture could be obtained in cases of chemical or mechanical irritation. We could obtain it in a number of cases of chronic appendicitis. Since the plastic of the mucosa, is conditioned by the juice content of the submucosa, it is to be expected that in dehydrated patients, a typical picture of the mucosa would be obtained. This expectation was confirmed in one of our cases where we had to deal with an individual 60 years of age who suffered from diarrhea for a considerable time.

He furthers his discussion in stating that the inflammatory or edematous swelling of the mucosa is expressed in an increased volume of the folds of the mucosa. One can readily see where these facts by roentgen pictures and sigmoidoscope aid in proper diagnosis and condition of the bowel; in ulcerative colitis the roentgen picture fails to show any structure of the mucosa, and only here and there irregular whitish spots pointing to is-
lands of mucosa, are seen. When such a colitis is healed the roentgen picture fails to show any folding of the mucosa, the latter resembling a paper-like structure, which is apparently unable to function normally. In the absence, then of the multitude of transverse and longitudinal folds as expressed above we have a normal bowel condition; so that the process of dialysis as the food is absorbed there is an exchange of waste material from the blood estimated to be about 12 per cent. We know the colon content is teeming with bacteria of all kinds. If something happens to change the chemistry of this bowel the non-virulent bacteria may become virulent so that it would be easier for one of the many disease producing germs to thrive and grow, in which event these bacteria or their toxins may become absorbed and be carried to all parts of the body.

The colon bacillus itself is non-pathogenic when the chemical or mechanical characteristics of the bowel are normal, but both Satterlee (9) and Bassler (10-11) have declared in a long and detailed manner that B. coli is an important etiological agent in ulcerative colitis. Bassler (11) has shown that a diffuse ulceration of the epithelial surface is possible, and he has traced the causative agent to the colon bacillus group. Under certain conditions an extremely virulent strain of B. coli may be developed, resembling the dysentery bacillus and producing symptoms somewhat similar to them. Torrey (12) isolated a strain of B. coli from each of twenty-five cases of ulcerative colitis. By a standard method he found that 13 might be regarded as virulent, and the remaining 12 strains as non-virulent. Paulson and Brown (13) found in their experimental work that B. coli isolated from a normal sigmoid, as well as, isolated from the
base of an ulcer in a sigmoid from the case of amoebic dysentery, produced similar lesions, grossly and histopathologically, in the intestines of laboratory animals to those produced by various types of streptococci isolated from ulcerative colitis. The latter experimentalists agree that there is no convincing experimental evidence on record that B. coli are of primary significance in the etiology of this process.

Brown (14) presents the following theory and states that Gross of Germany supports the same idea; that the chemical change is not the only factor as to virulence ascribed to normal bacterial inhabitants of the colon. They present the idea that for some unexplainable underlying reason, the local tissue resistance of the colon become lowered, and organisms that are habitual saprophytes take on an added virulence and become pathogenic. He says, "Is it not possible that the cause of the disease is to be found not in the presence of a definite and specific agent, but rather in the absence of some protective substance or mechanism, or of something which normally inhibits the bacterial invasion of the intestinal wall; perhaps due to some metabolic error, or endocrine disturbance or lack of a specific bacteriophage, or absence of some normal bactericidal substance in the intestinal mucosa?"

I believe that Brown's discussion of the lowered resistance of the local bowel tissue gives us no more clue to the etiological situation than a similar discussion on common colds. We take for granted that there must be a lowered resistance, but such a discussion is simply an impression and not an experimen-
al fact. In fact nothing is yet definitely known about predisposing factors. It has been said that debility and overwork may predispose to this condition, yet, on the other hand, chronic ulcerative colitis is seen frequently as an acute invasion in individuals in apparently perfect health.

In the past decade, more especially in the U.S.A. the consensus opinion seems to be that there is a definite and specific infective agent and therefore most all of the experimentalists are trying to isolate some specific strains. The bases for this conception lies partially in the bacteriological research done, by the pathology and symptomatology observed through all these years, and by the more recent interpretation of experimental physiology. The anatomist has aided the physiologist by closer dissection.

Even today, confusion exists between ulcerative colitis and tropical dysentery, and there are those who still assert that all cases of ulcerative colitis are examples of tropical dysentery. The viewpoint that chronic ulcerative colitis is an aberrant form of bacillary dysentery has been expressed most frequently by Hurst (15) of England, and has found many supporters in Great Britain, in Canada and in the United States. In fact, this viewpoint along with Bargen's isolated diplococcus are the two most accepted theories at the present time. It is because of the similar appearance, sigmoidoscopically, of bacillary dysentery and chronic ulcerative colitis, as well as the response to many cases following intravenous injection of polyvalent antisyntercric sera - a response which Hurst claims is not due to a
foreign protein inasmuch as similar results are not secured with
injections of immune horse serum - that cause him to revive the
suggestion of Saundby (16) and Hawkins (17) that chronic ulcerative colitis primarily is a B. dysenteriae infection. Thorlaks-
on and Cadham (18) Canada have reported recently that they have been able to isolate B. dysenteriae from the bases of ulcerations in a few cases by a special devised technique.

Both Thorlakson and Cadham realize the necessity of further study and state that the work bears confirmation. In the United States the consensus of opinion appears to be opposed to this theory. I found no cases from literature printed in this country where B. dysenteriae has been isolated from the stool or from ulcers through the sigmoidoscope. Hurst (15) explains this discrepancy by stating that B. dysenteriae is a very delicate organism and is greatly outnumbered by B. coli, hence the isolation of the former except at the onset of acute cases is extremely difficult. Paulson's (19-20) criticism is as follows: The facts which prevail and seem to operate against this notion are: the non-agglutination of the patient's serum with any of the known strains of B. dysentery, the contagiousness and easily transmissible character of bacillary dysentery, yet the extreme rarity of finding two cases of chronic ulcerative colitis either in the same family or in the immediate neighborhood; also the increase in the number of cases of this syndrome and the corresponding rarity in which true cases of bacillary dysentery are encountered in adults in the face of the greater knowledge, and improved diagnostic methods.
In 1924 and 1925, Bargen of the Mayo clinic (2) (22) (working under Rosenow and Rosenow's methods) presented the results of his experimental work in an effort to establish a gram-positive "diplococcus" as etiologically responsible for ulcerative colitis. He isolated 385 cases of Chronic Ulcerative Colitis presenting themselves for examination at the Mayo Clinic. In 266 cases of these the material obtained thru the proctoscope was cultered according to the method of Rosenow; a pneumococcus-like diplococcus of characteristic morphologic and biologic properties was isolated in 189(71%). Such an organism was always found in acute or subacute cases. Failure to obtain the organism in 29 per cent was due to the following causes: (a) chronicity with marked necrosis of mucosae; (b) overgrowth of the culture by saprophytes in many cases although the organisms were seen on direct smear, and (c) the impossibility in some of the latter cases of making more than one attempt at culture.

For the inoculations of animals the organism was injected as soon as the pure culture was obtained, or after the making of the primary glucose-brain-broth culture. Bargen stated that the elective localization in the animal's colon was thus strikingly demonstrated. He reports having injected 459 healthy rabbits. Lesions appeared in the colon of 131 of these varying from disseminated submucous hemorrhages to extensive ulcers of the colon. In 137 severe diarrhea ensued; evidence of the disease was thus found in a total of 268.
On the other hand Rosenow, Nickel, Meisser, Hufford, and Cook working along similar lines with other strains of streptococci, in the same laboratory, during the same time, with animals from the same common stock, have induced lesions in the colon only in rare instances, about two per cent. This, by the way, is the only control which Bargen has for comparison. He at no time ran controls himself.

At the present time there are a great number who oppose Bargen and his supporters, the greatest of which are Thorlakson, Paulson and Brown. In the literature there are innumerable reports and discourses as to the relative merits and results from the specific immune serum produced by Bargen. Thorlakson (18) states that his observations lead to the conclusion that Bargen's diplococci are important from the standpoint of perpetuating an ulcerative lesion in an already devitalized bowel and it is not the primary etiological factor. His opinion is that ulcerative colitis is an infectious disease due primarily to B. dysenteriae but influenced in its course by the streptococcus and other pathogenic intestinal bacteria. In 1928 Bargen presented a paper before the American Medical Association on etiology and treatment of ulcerative colitis. Smithies (24) stated, "I believe that I can describe a series of patients in whom the results of treatment without the employment of specific vaccines have been just as satisfactory as were those of which Dr. Bargen presented here, today, and included in my series are some which he and his associates have had under their care. I cannot subscribe
to Dr. Bargen's point of view. His vaccine has a place, but it cannot be classed as a specific curative agent for chronic ulcerative colitis.

Although Chronic Ulcerative Colitis had been described as a distinct entity, it was Wilks and Moxon (25) who first described it as a clinical entity in 1875. Prior to that time it was regarded as one of the end results of infection in other diseases. There was not such a great deal written about this condition until Bargen and Logan (26) in 1925 first published their description of the organism that bears Bargen's name, and since then Bargen has many agreeing with him and are trying his vaccine for treatment. There are, however, those who cannot agree with him either bacteriologically or get sufficient therapeutic results with his vaccine to warrant their acceptance; that this is the specific organism which causes ulcerative colitis.

In 1913 Bassler (27) gave the colon bacillus as the cause, and in 1927 he (28) stated that it was probably a hemolytic streptococcus. Just before Bargen published his view Yoemans (29), Brown (30), Wallis (31), Einhorn (32), and Thorlakson (33) considered the dysentery bacillus responsible, and up to the present time they do not agree with Bargen that he has isolated a specific organism.

The organism Bargen describes is a large, gram-positive, lancet-shaped diplococcus which has no capsule, grows aerobically on ordinary culture media, produces an alpha-hemolytic colony on blood agar, is not bile soluable,
does not ferment inulin, or Mannite, is not agglutinated by pneumococcus antisera, and produces antibodies in rabbits which agglutinate other strains, and is considered therefore to be biologically specific. The freshly isolated strains always ferments lactose. This organism is similar to the pneumococcus in morphology but differs culturally in that it(a) does not grow as well on ordinary media,(b) is soluble in bile,(c) ferments inulin,(d) does not ferment lactose, and (e) does not produce ulcerative colitis in animals whereas, Bargen's bacillus does in 60 per cent. Bargen's technic for isolation of the organism is given in (23).

As in all conditions where etiology is not clear, focal infection here too has been thought to play a role. Garvin (34) presents this view. The bases for his thought is dependent upon Mann and Williamson(35) and Eusterman(36). He states that since Hippocrates "cured" a rheumatic patient by extracting a tooth, interest in focal infection has been intermittently, more or less, in the foreground. Approximately 70% of patients consulting the general practitioner present complaints referable to the digestive tract. The relation between distant foci of infection and gastro-enterologic ailments, probably merits considerable discussion and consideration. For reference, that it might be understood on what he based his rather bold conclusion, refer to the first part of Garvin's(34) report. His conclusion: In view of the fact, therefore, of experimental evidence submitted, the clinical reactions, and the clinical improvement when foci of infection are removed, and
the rather good results emanating from the use of vaccine prepared from the diplococcus of Bargen, the significance of distant foci of infection in relation to etiology, at least, of ulcerative colitis cannot be overrated. How important they may be in its continuation, it is difficult to say, but their part in the early stages seem established. Bargen(23) has done some work along this line and shows some suggestive work which Garvin has attempted to carry on. The criticism which has been lent to the experimental efforts at the Mayo Clinic with regard to foci of infection is due to the fact that they have been using mixed cultures.

Eppinger and Hess(37) theory of vagatonia has been said to play some role in the etiology of chronic ulcerative colitis.

Brown(38) suggests that hyperperistalsis of the small intestine may be responsible for the whipping down of the duodenal enzymes to the colon, thereby causing ulceration there. Neither of these theories have been given any serious consideration.

The whole question bearing on recent studies of etiology of Ulcerative Colitis has become a problem of increasing interest and importance. Sir Humphrey Rolleston(39) feels that its etiology is still unknown and that it is a syndrome of fairly constant clinical manifestations and anatomic changes. The question of etiology is by no means settled, therefore in conclusion I shall again repeat the theories which have the greatest number of supporters. Conclusion: Considering the etiological factor as an in-
fectious agent there are four different views held, namely
that ulcerative colitis in this country is (a) due to
Bacillus dysenteriae, (b) due to specific strain of strepto-
coccus (Bargen), (c) due to the Bacillus coli communis of en-
hanced virulence (Bassler), (d) or due to many different
organisms which may vary with the individual case.

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apparently got the authority for his statements mostly from this article.


