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Etiology of ulcerative colitis : a historical review and appraisal of current concepts

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THE ETIOLOGY OF ULCERATIVE COLITIS: A HISTORICAL REVIEW AND APPRAISAL OF CURRENT CONCEPTS

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The etiology of chronic ulcerative colitis continues to elude discovery despite five decades of vigorous study by many investigators.

There are a number of obsticles to adequate study which have compounded the problem. Not the least of these is the absence of the disease in animals other than man. Many attempts have been made to establish the disease experimentally. Syndromes of bloody, mucoid diarrhea with sloughing of colonic mucosa have occurred, but no chronic, progressive disease has been produced. Also, the unpredictable course of the disease, with its remissions and exacerbations, the variability and multiplicity of its complications and its relatively low incidence complicate the picture and make study difficult.

EARLY HISTORY

The earliest description of ulcerative colitis was probably that of Sydenham in 1669, who recognized a diarrhea, different from ordinary dysentery, which tended to chronicity(121). In 1857 Oliver presented postmortem findings from three cases of chronic diarrhea, one of which may have been chronic ulcerative colitis(87). Sir Samuel Wilks is credited for the first written description in 1875(131).

CLINICAL COURSE AND PATHOLOGY

The onset of ulcerative colitis may be either sudden or insidious. Its course may be slowly progressive, with remissions and exacerbations over a period of years, rendering the patient chronically disabled, anemic and malnourished, or it may be rapid and fulminating. In the fulminating form there is a high fever, tachycardia, anorexia, severe anemia and profound debility. Death may result from perforation, massive hemorrhage, inanition and severe electrolyte imbalance(46). The most constant feature is bloody diarrhea, which may reach 20 or more evacuations daily.

The disease generally starts in the rectum or rectosignoid region and there is usually a retrograde extension of the process. A small percentage of cases have localized disease elsewhere in the colon and are depicted as segmental ulcerative colitis.

The pathologic changes depend primarily on the duration of the disease. Grossly in the early case there is marked hyperemia and edema of the mucous membrane, with small, irregular ulcerations. As the process progresses the ulcers tend to become confluent, with islands of mucosa remaining, giving the appearance of polyps. The final stage is characterized by

replacement of the muscular elements of the colon by fibrous connective tissue, resulting in rigidity of the wall and stricture formation(127).

Microscopically there is no consistent or characteristic pattern, but generally there is a diffuse cellular infiltration of lymphocytes, eosinophils and plasma cells, associated with edema and vascular congestion in the mucosa and submucosa. As the process progresses, similar changes are seen in the muscular coats, resulting, finally, in fibrosis(127). The basement membrane appears to be destroyed in many cases(57). Granulomas, with or without giant cells, are found in about 20 per cent of cases(41).

PROPOSED ETIOLOGIES

THE ROLE OF INFECTION

Microorganisms have received more investigation and support as the etiologic agent than any other cause. This is not surprising since the acutely ill patient, in a febrile, toxic state with an acutely inflammed, bleeding and sloughing colon, has all the characteristics of the individual ravaged by infection.

The recognition of infectious diarrhea as a specific entity reduced substantially the number of cases that might be considered ulcerative colitis. Except for the rare case of

ulcerative colitis which develops with or following the onset of bacillary dysentery, study of intestinal microorganisms has failed to reveal a clearly pathogenic strain. Fecal cultures yield the same organisms when obtained from ulcerative colitis patients as those from normal individuals and the difference is quantitative. Colony counts are increased 85 times over normal with coliform bacteria being increased 50 times(109). In 1950 Marshall, Kirsner and Palmer using sulfonamides were able to produce substantial decreases in bacterial counts but with disappointing clinical results. After prolonged treatment it was found that the counts returned to pretreatment levels(79). A study using Polymyxin B, Neomycin and Bacitracin revealed a similar reduction in bacterial counts, again without clinical improvement(58).

Bacillus Dysenteriae

The isolation and characterization of the dysentery bacillus of Shiga, in 1897, (113) produced a wave of enthusiasm for this agent as the cause of chronic ulcerative colitis(11, 38, 53, 55, 132). However, Sanndby in 1906 discounted attempts to separate ulcerative colitis and dysentery. He felt they were the same disease and isolated the Shiga bacillus from the feces of 6 patients with chronic diarrhea(108). In 1909, Hawkins published a detailed study in which he divided sporadic diarrheas into groups and recognized a group manifested

by a progressive chronic course, which he called chronic ulcerative colitis. Hawkins was unable to see any difference, except in duration, between acute dysentery and chronic ulcerative colitis, and despite his negative bacteriologic studies, concluded one was the chronic form of the other(48).

Hurst, in 1921, suggested that ulcerative colitis was a chronic form of acute bacillary dysentery, and he reported good results following treatment with a polyvalent antidysentery serum(53), but later stated that this may have been due to a nonspecific reaction representing nothing more than a form of protein shock(54).

Felson and Wolarsky studied the Jersey City epedemic of acute bacillary dysentery (1934) and found chronic diarrhea in 10.7 per cent of 122 cases, 9 to 12 months later. The same authors studied a group of World War II veterans with confirmed ulcerative colitis. Fecal cultures of 5 of 12 cases yielded dysentery bacilli at the beginning of their disease. Of 61 patients seen during their chronic phase, 6 had positive cultures of whom 1 had had a positive culture during the acute phase. This was considered significant since a control group had only 0.08 per cent positive cultures. They concluded ulcerative colitis was a chronic bacillary dysentery(32). In 1932, Mackie reported positive cultures in 20 per cent of 82 cases but concluded this suggested, but did not

establish an etiologic relationship(76).

Against this unitarian theory of the two diseases is the work of Brown and Bargen, who were able to demonstrate the bacillus in only 1 of 35 cases of ulcerative colitis(20); and Hern, who failed to get any positive cultures from 50 cases(50). The striking difference in characteristic age incidence between bacillary dysentery and ulcerative colitis also suggests separate etiologies(9).

Diplococcus and Diplostreptococcus

Bargen, in 1924, published what has become a classic in ulcerative colitis literature. He described a diplococcus isolated from the colonic lesions of 22 patients. When injected into rabbits this bacterium produced an acute hemorrhagic colitis in 56 of 190 rabbits(6). The gross pathology of these lesions was suggestive of acute ulcerative colitis, but microscopically there was a polymorphonuclear, not lymphocytic, infiltration. Bargan and Logan reported 80 per cent positive cultures for this diplococcus in 68 ulcerative colitis patients as compared with only 5 per cent of 20 normal individuals(7). They also found that animals fed a vitamin deficient diet were much more susceptible.

Cook isolated a diplostreptococcus similar to Bargan's from the infected teeth of ulcerative colitis patients. He was

able to produce colonic lesions, resembling those described by Bargen, in 60 per cent of 60 rabbits. He also inoculated the teeth of 15 dogs, 7 of which exhibited diarrhea, mucopurulent bloody discharges and colonic ulcers after 8 to 16 months. This reaction began as diarrhea without bloody pus and little or no ulceration. Later, the dogs developed "mucopurulent bloody discharges in great numbers, associated with rise in temperature, loss of appetite, loss of weight and strength and the development of numerous typical ulcers of the colon". Microscopically these ulcers showed hemorrhages, leukocytic infiltration, necrosis and ulceration(24). Ginsberg and Ivy felt Cook had succeeded in producing a fair approximation of the disease in his dogs(38).

The specificity of Bargen's organism was challenged by Paulson, who obtained 10 different strains of streptococcus from the stools of 14 ulcerative colitis patients. All of these produced ulcerative colonic disease in rabbits. He produced similar lesions by injecting rabbits with Escherichia coli, Shiga and Flexner strains of B. dysenteriae and dead cultures of hemolytic streptococcus from a case of puerperal sepsis. Paulson concluded the environment of the colitis colon favored the growth of streptococci(89). Monaghan(84), Kessel(61), Rafsky and Manheim(99) reached similar conclusions. Dack attributed these experimental

lesions to septic emboli and suspected they were present in other organs as well as the colon(25).

The controversy over the specificity of the organism has obcured the fact that lesions were produced and no attempt has been made to reproduce the work of Cook.

Staphylococcic and Pseudomembranous Enterocolitis

With the increasing use of broad spectrum antibiotics, such as Terramycin and Aureomycin, the entity of pseudomembranous enterocolitis, due to staphycoccal overgrowth, has become a prominent and feared complication. The gross and microscopic pathology of staphylococcic enterocolitis is nonspecific and consists of hyperemia, edema and extensive inflammatory necrosis. These lesions do not become chronic and generally respond to treatment with erythromycin(26). Pseudomembranous enterocolitis presents a superficial, green-black necrotic slough(125). Withdrawal of the offending agent will generally cure the condition. In addition to the clinical and pathologic differences, the recognition of ulcerative colitis long before the advent of antibiotics is evidence against an etiologic connection.

Viral Agents

Victor, Kirsner, and Palmer have reported an extensive survey in which they injected bacteria-free filtrates of feces and

rectal mucosa from patients with severe chronic ulcerative colitis into experimental animals(124). No lesions were produced with repeated intrarectal injections in monkeys or intracerebral and intraperitoneal injections into mice. No viral growth was demonstrated when fertile eggs were innoculated with the same material. They conceded, however, that their source of material may have been inappropriate and that their animals may not have been susceptible. Viral agents have not been excluded as possible etiologic agents, and further study is indicated.

Lymphopathia Venereum

Impressed with the clinical similarity between lymphopathia venereum and ulcerative colitis, Paulson postulated an etiologic relationship between them(91). He correlated positive Frie reactions in a high percentage of ulcerative colitis patients and prepared a bowel antigen which he felt gave positive results only in patients with positive Frie tests and ulcerative colitis(90, 92). Rodaniche, Kirsner and Palmer subsequently demonstrated negative Frie reactions in 22 out of 24 patients with ulcerative colitis, together with an absence of neutralizing serum antibodies against the virus of lymphopathia venereum. They concluded the only relationship between the two diseases was a superficial clinical resemblance(104).

Entameba Histolytica

Bernhoft has reported a series of 105 cases of proven amebic colitis, 2 of whom died of chronic diarrheal disease(12). The autopsy findings are described as "typical" of acute ulcerative colitis. He concludes there is an inherent tendency to ulcerative colitis, the latter being precipitated by amebic dysentery. No other reports of associated ulcerative colitis and amebic dysentery are available.

Bacterium necrophorum

Dack grew this non-sporulating saprophytic anerobe from 70 per cent of 298 patients with ulcerative colitis and from none of 99 normal controls. He found it to be the predominant organism in many patients with ileostomies during exacerbations of their colitis. Dack was unable to produce lesions in experimental animals with the organism and concluded it was probably a secondary invader(25).

Histoplasma Capsulatum and Other Fungi

Henderson, et al, reported a case of histoplasmosis which was characterized by chronic diarrhea and an ulcerative colitis(49). They reviewed the literature and found 8 of 25 reported cases of histoplasmosis had enteric manifestations. The pathologic picture is one of granuloma formation, and these authors suggest patients

with ulcerative colitis should be studied for histoplasmosis. No etiologic significance can be placed on these findings.

Swartz and Jaukelson isolated fungi from 87.5 per cent of patients with ulcerative colitis and 33.3 per cent of controls. The organisms were Geotricum in 66 per cent, Monilia albicans in 12.5 per cent and yeast-like organisms in 16.7 per cent(120). They suggested Geotrichum might be etiologically significant but there is no evidence to support this theory.

Bacteria as Secondary Invaders

It has been suggested that bacteria may be responsible for the chronicity of the disease after some unknown agent has caused the initial insult. In 1923, Rolleston suggested that dietary deficiencies reduced general bodily resistance, as well as the resistance of the colonic mucosa, allowing nonpathogenic organisms to invade and produce clinical infection(105). It is evident that many ulcerative colitis patients do not exhibit dietary deficiencies and conversely, the incidence of colitis in undernourished individuals is not greater than in well-fed people(75). Brown suggested bacteria gained their foothold due to the loss of some unknown protective substance or mechanism which normally inhibits bacterial invasion(21). Paulson postulated the bowel was rendered susceptible to bacterial invasion by some agent reaching

it by the hematogenous route(89). Felson extended this theory by indicting the dysentery toxin. He felt the toxin caused mucosal ulceration and enterococci and coliform organisms produced the chronic condition(31).

These concepts have needed revision since the use of antibiotics and the sulfonamides. Machella reviewed the literature dealing with almost 1500 patients. He found favorable results in 57.7 per cent with sulfonamides and 61.6 per cent with antibiotics(75). These results are no better than other forms of treatment not directed against infection. It seems clear that the role of bacteria in the production and maintenance of chronic ulcerative colitis has been far from clearly demonstrated.

DESTRUCTIVE ENZYMES AND SURFACE IRRITANTS

It is well recognized that the principal pathologic changes in ulcerative colitis are present in the mucosa. This led Warren and Sommers to postulate the presence of destructive enzymes(127). Lysozyme appeared to fit this theory well. This is a mucolytic enzyme discovered by Flemming. It is found in egg white, human tears, gastric juice and other secretions(33). The titre is increased in the stools of patients with chronic ulcerative colitis, increases during exacerbations of colitis and falls sharply with remissions, whether spontaneous or "induced". Meyer and co-workers

theorized that the enzyme denuded the colonic mucosa of its protective mucous covering, allowing bacterial agents and digestive enzymes to destroy the mucosa(80). Grace, Seton, Wolf and Wolff demonstrated increasing concentrations in the stools of ulcerative colitis patients during periods of anger, resentment, frustration and hostility and a prompt fall with the return of emotional calm(45). Meyer, et al, produced superficial ulcerative changes in the upper gastro-intestinal tracts of dogs fed large amounts of lysozyme by mouth(80). Prudden and co-workers found similar lesions in the colon of dogs given lysozyme orally and intra-arterially(98). Grace and his associates reported superficial inflammatory changes and edema by applying human tears to the colostomy mucosa of a patient with ulcerative colitis(45). Microscopic descriptions of these lesions are not part of the reports.

There are serious objections to accepting lysozyme as the cause of ulcerative colitis. Mickel and co-workers and Moeller, Klotz and Kirsner were unable to demonstrate persistent changes in various isolated sections of dog bowel by exposing them to concentrations of lysozyme as much as 10 times those found in the stools of ulcerative colitis patients(82, 88). Also, Moeller and Kirsner found the lysozyme titre to be increased in the rectal

washings of dogs following electrocautery of the bowel(81), and similar findings were reported by Moeller, Marshall and Kirsner following gastrointestinal injury with Mecholyl(83). These observers concluded the high lysozyme titres may be the result, rather than the cause, of ulcerative colitis.

Glass and his co-workers demonstrated the in vitro failure of lysozyme to exert a mucolytic or digestive action on mucous obtained from the colons of fistulous patients(39). Reifenstein, et al, determined the lysozyme titre in stools of ulcerative colitis patients and reported a significant reduction in titre following treatment with Aerosol OT, an antilysozyme compound, without concomitant clinical improvement(101, 102). They concluded lysozyme played no significant role in the pathogenesis of ulcerative colitis. Sammons and Hiatt, et al, demonstrated that the granulocyte was the source of lysozyme found in this disease and that it was released on dissolution of the granulocyte body(51, 107).

These studies indicate there is probably no etiologic relationship between lysozyme and ulcerative colitis. The enzyme is a reflection of the degree of purulent exudation(51, 107).

Lysozyme is one of a large group of proteolytic factors in normal and pathologic feces. Warren and Sommers studied the

proteolytic activity of the stools of 9 patients with ulcerative colitis, as well as that of patients with other intestinal diseases and individuals without demonstrable gastrointestinal disease. They found markedly increased proteolytic activity in 2 patients with ulcerative colitis, but also in single cases of peptic ulcer, enteritis, irritable colon and colelithiasis. They felt the findings were significant but conceded the nonspecificity of their factor(126). Stoughton has demonstrated a cytolytic factor in fecal filtrates from patients with ulcerative colitis which has a disintegrating effect on human epidermis. Ther factor was found only in the feces of patients with ulcerative colitis and was distinquishable from trypsin(115).

Unfortunately, this fragmentary knowledge of enzymes is too scant to allow any conclusions, but does indicate a neglected field worthy of further investigation.

Bile, Pancreatic Juice and Intestinal Enzymes

The preceding discussion has dealt with abnormal enzymes. There is some evidence concerning the normal enzymatic constituents of the gastrointestinal tract. Portis, Block and Necheles suggested that hypermotility of the small bowel might bring pancreatic trypsin to the colon before it was inactivated; and they demonstrated that 1 or 2 per cent trypsin solution produced changes

in colonic mucosa consisting of hyperemia and edema(97). Ivy and Clarke were unable to produce any changes in dog colons following 6 to 23 weeks of drainage of bile and pancreatic juice directly into the appendix and colon(56). Lake, et al, transplanted loops of colon into the duodenum of dogs and were unable to demonstrate any injury(70). They also recorded normal volume and composition of pancreatic juice in patients with active ulcerative colitis. It is also known that in patients with isolated colons, following ileostomy, the process continues. Ball, Baggenstoss and Bargen observed chronic interstitial pancreatitis in about half of patients with ulcerative colitis, indicating decreased secretory activity(5). If pancreatic enzymes were important in the pathogenesis of ulcerative colitis, hyperplasia would be expected.

NUTRITIONAL DEFICIENCY

In contradistinction to the theories concerning enzymatic destruction by excessive normal or abnormal enzymes are those which postulate a lack of protective enzymes of antiproteolytic substances(37). This theory rests entirely on a small amount of evidence gained by therapy with extracts of hog gastrointestinal tract. Streicher(116), Streicher, Grossman and Ivy(117), and Freidman and Haskell(36) have reported 35 to 89 per cent good

results using various extracts. These results are similar to those obtained with other forms of treatment and lend little support to the proposal.

An acute hemorrhagic ulcerative colitis has been noted to occur in occasional patients being treated for far advanced neoplastic disease using folic acid antagonists (Aminopterin)(122). Rinehart and Greenberg subjected monkeys to folic acid deficient diets and described an ulcerative colitis which in its end stages resembled late ulcerative colitis in humans(103). The acute change is one of metaplasia, rather than suppuration, and is not suggestive of the disease in man. The disease does not appear to be associated to a significant extent with other dietary deficiency states(75).

Lymphatic Obstruction

Reichert and Mothes suggested lymphatic obstruction as the pathogenetic mechanism in ulcerative colitis, and attempted to produce the disease by injecting sclerosing and irritating agents into the mesentenic and submucosal lymphatics of animals. Chronic lymphedema resulted without slough or bleeding(100). Poppe reported edema, inflammation, bleeding, cellular necrosis and acute ulceration(95). Sinaika and Necheles produced ulceration in only one of their animals(112). They concluded ulcerative colitis

was not due to lymphatic obstruction and the theory has not been investigated further.

PSYCHOSOMATIC FACTORS

Murray(85) and Sullivan and Chandler(119) first pointed out the relation between a disturbed psyche and ulcerative colitis. A detailed consideration of these relationships is beyond the scope of this paper since they are largely theoretical and sparsely supported by good experimental evidence. Certain highlights are essential, however, if a complete picture of the etiologic possibilities in the pathogenesis of ulcerative colitis is to be gained.

Muscular Spasm

Lium published experimental evidence in support of his concept of muscular spasm as the basic etiologic process in ulcerative colitis. He felt this was an exaggeration of normal reflex defecation(72, 73). Ginsberg and Ivy object to this concept. They feel there should be more ulceration in cases of diarrhea, mucous colitis and spastic colon if spasm is ulcerogenic(38). Numerous investigators have studied the motor phenomena of the colon using various pressure recording devices(1, 23, 59, 114). It has been noted that there is an overall reduction in bowel motility with a substantial decrease in mixing and absorption-inducing motility. This loss is partially made up by the appearance of

powerful, propulsive, excretory mass movements (Type IV waves) (59,114). Grace, Wolf and Wolff reported similar contractions with their observations on ulcerative colitis patients with colostomies when the patients were disturbed by life situations provocative of anger, resentment, hostility or anxiety(46).

Vascular Factors

Vascular changes have been described which may have bearing on the etiology of ulcerative colitis. Drury, Florey and Florey described a mucosal blanching reaction during fright in dogs(27). Freidman and Snape observed blanching of the mucosa of the colostomies in 3 children, in whom no colonic disease was present, when the children were exposed to mildly painful stimuli or to the discussion of past unpleasant experience(35). Wener and Polonsky observed that the colon participated in general bodily reactions in conjunction with life situations. There was pallor and decreased motility associated with reactions to pain, fear and anxiety, and when the patient was resentful, angry or hostile, the bowel became hypermotile and the mucosa was hyperemic, edematous, bled easily and scattered petechiae appeared(130). They interpreted these findings as indicating a vascular origin to ulcerative colitis, but conceded muscular spasm might also contribute to the process.

Autonomic Nervous System

In connection with these motor and vascular phenomena, efforts have been made to demonstrate an autonomic imbalance in ulcerative colitis. Portis viewed ulcerative colitis as the result of cholinergic predominence arising from sacral parasympathetic overstimulation(96). Several groups have used parasympathetic drugs by various routes in an effort to produce ulcerative colitis in dogs(60, 81, 129). Noteworthy in this regard is the fact that no microscopic differences were seen in the colons of dogs sustained for longer than one year and those treated only briefly(60). These findings are in accord with, but do not establish, the concept of parasympathetic overstimulation in the pathogenesis or chronicity of ulcerative colitis.

The role of the sympathetic nervous system has not been studied, but Yorkman suggests that this system is implicated by its effects on blood vessels(133). He states that edema results from pre-capillary and, probably, venous contriction, both sympathetic phenomena. Schlitt and co-workers were sufficiently impressed with the role of the autonomic nervous system to attempt treatment by pelvic autonomic neurectomy(110, 111). They demonstrated some improvement in the tendance to formed stools and weight gain, but the patient's disease remained progressive.

Psychiatric Factors

Certain personality traits have long impressed psychiatrists as being frequent and probably characteristic(29, 30). The individual is usually described as being abnormally dependent on others with a diminished ability to tolerate frustration or to assume responsibility, summed up in the term "immature". In a study of 20 patients with ulcerative colitis, Mahoney, et al, contend that the neurotic and immature traits existed before the development of colonic disease and were not the result of it(78).

Psycho-biologic mechanisms that result in ulceration of the colon remain to be demonstrated. Some writers state it is secondary bacterial invasion and/or enzymatic destruction which is allowed to overcome normal protective mechanisms by the changes present during the psychic onslaught(29, 30, 118). No experimental evidence exists to support these theories, and "....the bridging of the gap between psyche and soma remains purely a conceptual one"(125).

ALLERGY AND HYPERSENSITIVITY

Gastrointestinal Allergy

The gastrointestinal tract was first implicated as a target organ for allergic reactions by Andresen in 1925(2). In 1942 the same author reported that 33 per cent of his 50 patients showed

allergic reactions to foods and responded favorably to dietary management(3). Rowe(106) and Mackie(77) reported 50 per cent and 60 per cent responses to removal of allergenic foods from the diets of ulcerative colitis. These figures are less significant than they might seem since they are similar to those reported with other forms of treatment. Grey and Walzer passively sensitized rectal mucosa by injecting human reagin-bearing serum intramucosally, followed by oral or topically applied allergen. A sharp inflammatory reaction occurred, resulting in edema, hyperemia and increased mucous secretion. The reaction was transient and ulceration did not occur(47). Bassler found allergy significant in only 20 per cent of his patients(10) and Paulley reported the incidence of allergic disease in his series to be only slightly higher than in the general population(96). Monaghan carried out a large series of signoidoscopic observations after feeding foods suspected of being allergens and found only a rare instance in which damage could be noted(84).

Hypersensitivity

In recent years many investigators have been impressed by the compatibility of the clinical and pathologic findings in ulcerative colitis with a hypersensitive etiology. The frequency and spectrum of extra-colonic complications are suggestive of hypersensitivity.

Such entities as erythema nodosum, urticaria, periarteritis, scleroderma, rheumatic fever, hemolytic anemia, lupus erythematosis, uveitis, arthritis and hepatic, renal, endocardial and myocardial damage are relative common(8,13,19,34,40,52, 69,74,128). There is a high incidence of complications, allergic in nature, associated with blood transfusions and drugs(64).

The changes seen in the serum protein factors have been considered suggestive of hypersensitivity(69), but more recent evidence indicates these changes may be the result of losses through the colonic mucosa and secondary to infection. The favorable responses to ACTH and adrenal corticosteroids, and the age incidence are considered significant by Kirsner(64).

Experimental studies concerning the immunologic capabilities of the colon have come from several investigators. Anatomically, the colon possesses an abundance of lymphoid tissue, plasma cells, and mast cells, considered by most immunologists to be potent sources of antibody. The latter are known to elaborate serotonin, histamine and "capillary permeability factor," substances frequently implicated in allergic and hypersensitivity reactions(64).

Experimentally, Goldgraber and Kirsner have reported the production of classic Arthus and Shwartzman reactions in the colon

of rabbits, with the same histologic changes noted in the skin, that is, cellular infiltrates, superficial ulcerations and granuloma formation, apparently similar to the histologic changes in ulcerative colitis(42,43). Of interest is the utilization of the Auer phenomenon in the production of ulcerative disease in the rabbit colon(28,63,65,66). This reaction is based on the fact that generalized antigen-antibody reactions tend to localize in areas of injury(28).

If ulcerative colitis is an immunologic disease, then antibody to some specific colonic substance, serving as an antigen, must be present. There is a rapidly growing volume of literature concerning circulating anti-colon substances from the sera of ulcerative colitis patients. These antibodies are being studied by a wide variety of methods. Broberger and Perlmann have demonstrated precipitating and hemagglutinating antibodies in the sera of most of their patients, which were not detectable in normal controls(18). These antibodies were not completely specific and occasional cross-reactions were obtained with extracts of liver and kidney. In addition to precipitin and hemagglutination reactions, these antibodies have been subjected to study by ager-gel diffusion, flourescent antibody, and complement-fixation techniques by several investigators with general agreement concerning their

presence and nature(4,15,16,17,68,86,93,94,123).

Several objections have been raised to an immunologic mechanism as the etiology of ulcerative colitis. It has not been demonstrated that antibody occurs before, or even with, the development of disease and the possibility is suggested that these substances may occur as a result of the destructive process, rather than its cause. Also, the antigen or antigens have not been identified. The current research has been carried out using highly impure substances as antigen, leaving some reasonable doubt as to their specificity, origin, and nature.

Kirsner has formulated what appears to be a reasonable group of criteria which he feels should be met before the role of auto-immunity can be adequately evaluated(64). These are, in essence:

1. A hypersensitive patient,
2. Circulating or cell bound antibodies, active at body temperature, at the onset of the illness,
3. Characterization of specific antigen or antigens,
4. Experimental production of antibody,
5. Possibly evidence of alteration of tissue by bacterial, viral, chemical, physical, or pharmacologic agents, rendering it antigenic,

6. Possibly evidence of a characteristic alteration in the colon,
7. Localization of specific antibody in the colon,
8. Consistent production, by means of specific antibody, of similar disease in animals,
9. Absence of similar changes with antisera against tissue other than colon, and
10. Possibly effective treatment with agents which suppress the antigen-antibody reaction.

DISCUSSION

Ulcerative colitis is a severe debilitating disease affecting many organs in addition to the colon(127). The variability of its onset, course, complications and responses to therapeutic attempts have complicated efforts to establish an etiology.

Extensive attempts to uncover infectious agents have generally failed to withstand careful study. The various bacteria claimed to cause ulcerative colitis must be considered secondary invaders, although there are areas which need more study. The significance of bacteria as secondary invaders also remains to be demonstrated.

Ulcerative colitis has been considered to be the result of

enzymatic abnormalities. After extensive study lysozyme cannot be held responsible, since it does not show significant mucinolytic or proteolytic properties. The high titres found in ulcerative colitis can be attributed to, and correlated with, the degree of purulent exudation. There is some evidence to indicate other enzymatic substances may be important. These compounds need further purification and characterization before conclusions can be drawn regarding their significance.

Abnormal mental states are common in patients with ulcerative colitis. Attempts have been made to classify these abnormalities, but there is no adequate explanation of a psycho-biologic mechanism. The proposed theories are largely conceptual and without experimental or clinical support. There is strong suggestive evidence that the autonomic nervous system may be involved.

There are numerous characteristics of ulcerative colitis which suggest an antigen-antibody reaction in its pathogenesis and course. This mechanism may be a type of Auer phenomenon with food allergens inducing the reaction, but clinical attempts to remove such allergens are not completely satisfactory. Circulating antibodies to extracts of human colon have been demonstrated in the sera of many ulcerative colitis patients, suggesting an auto-immune

mechanism. This evidence is fragmentary at present, and further investigation is needed.

CONCLUSIONS

Ulcerative colitis is a disease of unknown etiology. Bacterial agents are not the sole cause, but more study is indicated, especially of possible viral agents. The work started by Cook deserves confirmation(24). The role of secondary invasion by intestinal bacteria is not clear.

Proteolytic and mucinolytic enzymes probably do not play a significant part in the initiation of ulcerative colitis.

Emotional factors mediated through the autonomic nervous system may contribute by increasing susceptibility to some other insult. No adequate psycho-biologic mechanism has been demonstrated.

The role of antigen-antibody reactions in the course of ulcerative colitis is under active investigation. Clinical, pathologic and experimental evidence is highly suggestive of hypersensitivity. No etiologic significance can be assigned these phenomena on the basis of current evidence.

SUMMARY

1. The proposed etiologic mechanisms in ulcerative colitis have been reviewed. The clinical, pathologic and experimental

evidence has been considered in an effort to clarify the many theories.

2. No proposal has been demonstrated to withstand careful examination, and the etiology remains unknown.

3. Hypersensitivity is under active investigation and may eventually provide the answer, however, the criteria are strict and much work will be needed before any conclusive statement can be made.

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