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Although several measurements of both cellular and humoral immunity are altered in inflammatory bowel disease (IBD), no direct pathogenic role can be confirmed in either ulcerative colitis (UC) or Crohn's disease (CD). No clear role has been shown for allergic, microbiological, or psychogenic factors, and no specific genetic susceptibility has been demonstrated.

Several studies have shown some benefit from using immunosuppressive drugs to treat inflammatory bowel disease, such as sulfasalazine to treat ulcerative colitis and corticosteroids to treat Crohn's disease. Whether these benefits derive from the anti-inflammatory activity of these drugs or from their immunological effects is uncertain.

In the United States, the incidence of inflammatory bowel disease, e.g., Crohn's disease (CD) and ulcerative colitis (UC), is estimated at 500,000 to 2 million (1). The frequency and prevalence of Crohn's disease is increasing, while the incidence of ulcerative colitis appears to have stabilized.

The etiology of both Crohn's disease and ulcerative colitis remains obscure. Several mechanisms have been proposed, including infectious processes by bacteria or viruses, immune mechanisms, genetic factors, abnormalities of the lymphoid cell system and of the intestinal lymphatics, and psychogenic factors.

Psychogenic factors appear to play a secondary rather than a primary role in both types of inflammatory bowel disease (IBD). Although significant emotional events may trigger an episode of ulcerative colitis, there is not enough objective evidence to substantiate a direct causal relationship, especially since medical and/or surgical treatment can successfully resolve the problems associated with this disease. Emotional stresses are also implicated in the recurrence of Crohn's disease, although their direct role in its pathogenesis is unlikely, based on current knowledge.

Unfortunately, no experimental model exists for either Crohn's disease or ulcerative colitis.

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Histology

In ulcerative colitis, the inflammatory process primarily involves the colonic mucosa and submucosa, which consist of infiltrates of both lymphocytes and plasma cells and, to a lesser extent, eosinophils and polymorphonuclear cells (2). MAST cells and plasma cells are also increased, with an alteration in the ratio of IgG-to-IgA plasma cells from a normal ratio of 1/20 to an abnormal ratio of 4/1. C3 has been shown at the basement membrane of epithelial cells. Reactive hyperplasia may be seen in regional lymph node cells.

The earliest lesions in Crohn's disease, which is a full transmural inflammation of the colon, are aphthoid ulcerations often located over lymphoid aggregates with subsequent lymphatic obstruction, lymphocytic infiltration, and edema. Although granulomatous tissue reaction can occur, 30-40% of Crohn's patients may not have any detectable granuloma.

Allergic Factors

At present, no clear role has been found for allergic factors in inflammatory bowel disease. In one study, no significant difference in a personal or family history of atopic disease existed between 74 IBD patients (39 with ulcerative colitis, 35 with Crohn's disease) and a control group. IgE levels, as well, did not differ. Patients with inflammatory bowel disease tended to have more positive prick tests to food, especially eggs, milk, and cereals, but the total number of skin tests did not significantly differ. These results likely reflect only increased absorption of food antigens. However, atopy is suggested by the finding of increased tissue

and peripheral eosinophilia and greater numbers of IgE plasma cells in the rectal mucosa of patients with proctitis. It has also been suggested that sodium cromoglycate, which is a MAST cell stabilizer, has a beneficial effect on inflammatory bowel disease (3).

Microbiological Factors

In ulcerative colitis and Crohn's disease, gut bacterial counts are increased for both aerobic and anaerobic bacteria, which may contribute to the inflammatory reaction in the bowel. Bacterial possibilities include bacteriodes and E. coli. In Crohn's disease, the anaerobic Yersinia enterocolitica has been isolated in some cases.

In 1970, Mitchell and Rees (4) induced granulomas in mice by injecting their foot pads with intestinal tissue and mesenteric lymph node homogenates from Crohn's disease patients; however, the process took up to 500 days. A transmissible agent, which appears to be a picornavirus, has been found in Crohn's disease patients. It is heat stable, can withstand freezing up to −70°, and is sensitive to autoclaving. A separate agent for ulcerative colitis has also been found.

Parent and Mitchell (5) have recently shown a cell wall defective, pseudomonas-like organism in eight of eight patients with Crohn's disease by culturing biopsy material in hypertonic media before filtration. However, they could not demonstrate it in nine patients with ulcerative colitis or in 20 control patients who did not have inflammatory bowel disease (colon carcinoma, colon polyps, endometriosis, vascular malformation, pancreatic carcinoma). Few clinical diseases have been shown to be due to cell wall defective bacteria, and parent organisms could not be shown in the tissues studied (5). Cell wall defective bacteria may arise via antibody plus complement, or by antibiotic exposure, and generally revert to parental form in order to produce disease. They evade cell wall directed bacteriocidal antibiotics (penicillins, cephalosporins); they may even reside within red blood cells and hence escape lymphocyte action. They may also persist in polymorphonuclear cells or macrophages or revert to their parent forms.

Cell wall defective bacteria, with their slower replicating rate, present a less acute antigenic challenge that results in more prolonged exposure to immunogenic cells and higher antibody levels. If immune complexes were formed in slight antibody excess or at equivalence (equal antigen and antibody amounts), then granulomatous inflammation, as seen in Crohn's disease, would be favored (6). The neutrophil defect seen in some patients (7-9) may contribute to granuloma formation by producing a situation analogous to the chronic granulomatous disease of childhood.

Kagnoff (10) in an editorial pointed out that Parent and Mitchell performed their study without a screened control group and without using a neomycin-erythromycin bowel preparation before surgery. The high levels of serum lysozyme found in Crohn's patients may also produce cell wall variants. Antibiotics such as tetracyline, which are effective against cell wall defective bacteria, are not consistently effective in managing inflammatory bowel disease (10).

Genetic Factors

In 15-20% of patients with inflamatory bowel disease, genetic factors are suggestive (1). In some cases, the disease has occurred in three or more members of the same family over three generations. It also occurs in monozygotic twins with an increased concordance ratio. A strong genetic predisposition also exists in the patients who have both inflammatory bowel disease and ankylosing spondylitis. The genetic factor may be a polygenic type of inheritance that primes a susceptible person to develop inflammatory bowel disease given the appropriate environmental, emotional, or infectious stresses. No specific HLA types have been associated with inflammatory bowel disease other than the HLA-B27 of ankylosing spondylitis. The occurrence of inflammatory bowel disease in families, however, may reflect only common antigenic exposure.

In a recent study (11), lymphocytotoxic antibodies were detected in 27 of 53 patients (51%) versus 11 of 53 (11%) controls and in 23 of 53 (43%) patient spouses versus 3 of 53 control spouses (6%). Lymphocytotoxic antibodies are formed in response to and are markers of the presence of an infectious agent either through sharing of antigenic determinants with surface membrane determinants on lymphocytes or through interference by the agent with the normal state of tolerance to such determinants. These antibodies are cold reactive with maximum activity at 15°C. They are non-HLA-dependent, reacting predominantly to T cells of the IgG or IgM class. They are seen in acute viral infections such as infectious mononucleosis and systemic lupus erythematosus. There is no relationship between their titer and disease activity, duration, extent, or treatment mode.

In a study from Israel (12), 53.5% of 60 Jewish patients with ulcerative colitis were found to be HLA-Bw35 positive versus 30.6% of controls. There was also a suggestion that HLA-AW 24 was associated with an earlier onset and more severe disease. However, Crohn's disease patients did not show any significant correlations in terms of HLA antigen differences when compared to a control population. The same study showed that the frequency of HLA-Bw35 increased in patients with myasthenia gravis, rheumatic fever, atopic dermatitis, subacute thyroiditis, Grave's disease, and

necrotizing venulitis (12). This finding suggests a possible association between specific immune response genes and HL-A antigens that may be more evident in this Israeli population than in the U.S. population. Genetic factors in Crohn's disease have also recently been shown in studies of kindreds with this disease (13).

Immunological Mechanisms in Inflammatory Bowel Disease

In 1964 Palmer and Kirsner (14) first proposed a possible role for immune mechanisms in producing the lesions of inflammatory bowel disease. However, experimental attempts to reproduce these lesions by immune mechanisms have so far failed. There is no good animal model. The finding of colonic ulcerations by colonoscopy in patients with systemic lupus erythematosus is of interest, though, as they are similar to those seen in the early stages of Crohn's disease.

Humoral immunity

No specific immunoglobulin abnormalities have been found in either ulcerative colitis or Crohn's disease. The normal ratio (10/1/1) of IgA/IgG/IgM-bearing cells in the lamina propria is altered in inflammatory bowel disease, and plasma cells are found in the deeper layers of the bowel wall where they are not normally found. It has been reported that IgG levels are higher in ulcerative colitis and IgM levels are lower in Crohn's disease; however, in a study of 93 patients with ulcerative colitis (65 patients with Crohn's disease and 53 hospitalized control patients), the mean level of all immunoglobulins was significantly elevated, while only the IgM level was significantly raised in Crohn's disease (15).

In one study of Crohn's disease (16), granulomas were seen predominantly in the medullary cords (a B cell area of lymph nodes) and only occasionally in the paracortical areas (T cell area). Within the granulomas, though, macrophages were seen. This study suggests that the infiltrate in Crohn's disease is composed primarily of B cells with some T cell modulation.

Chronic gut inflammation may stimulate antibody formation against antigens in the gut lumen resulting in the production of antibodies to both bacterial and dietary antigens. This local antibody production may spill over into the systemic circulation. Inflammation may increase the permeability of the mucosa to antigens and contribute to the hypergammaglobulinemia, especially with colon involvement, as bacterial counts are significantly higher. Engstrom, et al (17) have reported on one family with secretory piece deficiency (and hence no secretory IgA) with inflammatory bowel disease. In this instance, the lack of IgA might increase susceptibility to infection or permit bacterial antigens to invade the mucosa.

An antigen to human colon has also been isolated from the colon and cecum of germ-free rats that is gastrointestinal-specific but not colon-specific. Antibodies against this antigen cross-react with E. coli 014 lipopolysaccharide antigens, not only in patients with ulcerative colitis or Crohn's disease, but also in relatives of IBD patients who do not have the disease. However, these colon antibodies do not correlate with duration, extent, severity of the bowel disease, age, or the sex of the patient. They cannot be identified in involved tissues, they are not cytotoxic to fetal colonic epithelial cells in culture (even with added complement), and they can persist after colectomy for two to ten years. These antibodies may represent only the increased bacterial absorption that follows mucosal inflammation, as the same antibodies can be produced after salmonella and shigella colitis (18). Moreover, when Heddle and Shearman compared antibody levels to E. coli 014 in patients with ulcerative colitis and in a control population, no increase was found (18). Consequently, it is likely that these antibodies have a secondary role.

In one third of patients with ulcerative colitis and Crohn's disease, one can demonstrate circulating immune complexes by the technique of inhibition of antibody-dependent cellular cytotoxicity (19). Other studies that used the ^{125}I $C1_q$ precipitation technique showed that immune complexes were present in up to 85% of patients with active disease. However, this method can give false positive results through its binding with single-stranded DNA or endotoxin (19).

Although both IgG and IgM can be produced locally from mucosal plasma cells, the nature of the antigen remains unknown. IgG, C3, and C1q have been shown by means of immunofluorescence on the surface epithelial cells of the colon at basement membrane level. In one animal study (20), rabbits with formalin-induced, rectal mucosal damage were given human serum albumin/anti-human serum albumin intravenously. The result was a form of colitis histologically similar to human ulcerative colitis, including the presence of crypt abscesses. Hodgson (20) suggests that if acute colitis is severe enough to allow gut-associated antigens to be adequately absorbed, then the patient's hypersensitivity to colonic bacteria (possibly enhanced by a genetically programmed host) could allow the disease to become chronic.

Levels of immune complexes in Crohn's disease also appear to correlate with disease activity and extraintestinal features. According to Lawley, et al (21), they are more common in patients with colonic involvement and disap-

pear after the diseased bowel has been resected. These investigators found no correlation between antibody levels to E. coli and the degree of local inflammation in either disease (21). Patients with positive immune complexes have also shown increased eosinophilia in both colonic mucosa and mucus (22).

Cellular immunity

Delayed hypersensitivity skin tests, in general, have the same pattern (either hypersensitive or anergic) in both normal individuals and in patients with inflammatory bowel disease. Up to 70% of Crohn's disease patients are anergic to dinitrochlorobenzene (DNCB) versus 5% of controls, and 50% are anergic to other skin test antigens such as purified protein derivative (PPD) and streptokinase-streptodornase (SK/SD). In a recent study (23), only two of 10 patients with Crohn's disease had one or more positive hypersensitivity skin tests at 43 hours (<10 mm induration). The eight who did not respond were given 1200 mg of the antihistamine cimetidine in divided daily doses and then were retested one month later. At that time, seven of the eight had one or more positive tests (especially to SK/SD), although no clinical changes were evident (23). It is known that histamine by means of negative feedback via H2 receptors on lymphocytes elevates c'AMP levels and suppresses lymphocyte function. If the H2 antihistamine cimetidine blocked this action, then increased delayed hypersensitivity would be seen (23). Whether a month is long enough to assess an effect on clinical activity is not known but may be worth further study.

T cell subgroups (helper cells, suppressor K cells) are in normal proportions in ulcerative colitis, although their total numbers may be reduced, presumably from their loss into the gut. Crohn's patients may have both decreased numbers and proportions of T cells either from enteric loss or sequestration within the deeper layers of the bowel wall (24). The T cell levels, however, return to normal when disease remits. Other studies show that cell-mediated immunity is normal in the early stages of Crohn's disease and declines only with long-standing disease (24).

Mitogenic stimulation with PHA (phytohemagglutinin) is normal in ulcerative colitis, although it has been reported as reduced in Crohn's disease patients (25), and in some cases it may persist at a low level in spite of medical therapy or surgery to eliminate the diseased bowel. Although this suggests a primary defect in cell-mediated immunity in Crohn's disease, there is no correlation with disease activity or duration of illness (25).

In the early stages of Crohn's disease, the mixed lymphocyte culture responsiveness of peripheral blood lymphocytes is normal, yet some decreased function has been shown in long-standing disease (26). Lymphocytes also have a cytotoxic effect on colonic epithelial cells that is found only in inflammatory bowel disease, although there is no cytotoxicity to gastric and ileal cells. This effect is rapid, tissue-specific, and does not require complement; it can also be produced by cell-free filtrates. It disappears within 10 days after colectomy (ulcerative colitis) or resection (Crohn's disease), but returns if Crohn's disease recurs. One can block this cytotoxicity by preincubation with anti-T cell anti-sera or by preincubation with E. coli 0119 B14 lipopolysaccharide. It is transferable by the patient's sera via IgM antibody or via sensitized T cells (K cells) which are armed by immune complexes with free antibody (antibody excess).

Hodgson, et al (27) looked at the conconavalin-A-stimulated suppressor cell activity of peripheral mononuclear cells in 11 patients with ulcerative colitis or Crohn's disease. In both healthy and hospitalized controls, the allogeneic lymphocyte-induced blast transformation was suppressed by 27.4%, but in the patients with inflammatory bowel disease it was suppressed by 9.2% ($P<0.005$). Five patients showed a helper effect. The degree of suppression correlated with disease activity: the more severe the disease, the higher the rate of suppression. One patient with toxic megacolon who was followed serially had a disease remission before normal suppressor function returned. This suggests that the loss of suppressor function might allow inflammation to persist by failing to control immune responsiveness.

Measuring cellular immunity in IBD patients presents many technical problems. Paramount among them is the use of crude antigens, since the specific antigens are not known. Timing is also important in terms of disease activity, duration, and treatment, as are considerations such as a deficiency of folic acid, which is required for blast cell transformation (27).

Complement levels

In one study of 93 patients with ulcerative colitis, 66 with Crohn's disease, 20 healthy controls, and 31 hospitalized patient controls (ulcer, disc disease), the levels of C3, C4, and $C1_q$ factor B (C3 proactivator) were measured (29). In the IBD patients, levels of all complements except C4 were higher. In general, the more extensive the colonic disease, the higher were the C3 and factor B levels. These were not affected by steroids or by skin, joint, or eye complications. Patients with liver disease had significantly lower C4 levels, while those patients with immune complexes had higher levels of C3 and factor B. Since neither C3c nor C3d was found, the pattern of rise of these proteins is that of acute phase reactants (29). In the immune complexes of ulcera-

tive colitis and Crohn's disease patients, the C3 conversion products increased, as did the C3 fractional catabolic rate.

Some investigators have also shown alternate pathway activation (low properdin levels). Lake, et al (30) performed a prospective study of 32 patients with inflammatory bowel disease at the time of diagnosis and before therapy was started. Although classical pathway components indicated normal levels and function, patients with extraintestinal manifestations of inflammatory bowel disease had low levels of properdin and properdin convertase, while patients whose disease was confined to the colon had normal levels. Although these findings may reflect only inflammatory activity, IgA and/or IgE complexes may play a role.

Skin Reactivity and Phagocytic Function of Neutrophils

In general, delayed hypersensitivity skin tests of IBD patients cannot be used to predict the clinical course of the disease reliably (31). In one study (31), 43 patients with Crohn's disease, 20 with ulcerative colitis, and 54 controls with minor skin diseases or urticaria were tested intradermally with various bacterial antigens. Crohn's disease patients as a group tended to have more positive reactions but not to any specific antigen. In another study (32), the phagocytic index for yeast particles of Crohn's disease patients versus controls was low, especially if the ileum was involved, whereas the phagocytic index of ulcerative colitis patients was the same as for the control group.

The nitroblue tetrazolium test has produced conflicting results. In one study (7), the results were normal for both Crohn's disease and ulcerative colitis patients, whereas in another study the test scores were low (8). However, these low scores were felt to be related to the presence of immune complexes in these patients, since immune complexes have been shown to elevate low test scores by neutrophils. In the former study (7), the skin window technique was used on Crohn's disease patients to demonstrate defective neutrophil migration, although in vitro tests (chemotaxis assays) showed that polymorphonuclear function was normal. Monocyte accumulation, though, was normal at 24 hours in the assays. This abnormal acute inflammatory response could lead to antigen persistence and predispose to chronic inflammation (6).

The Immunological Role of the Gastrointestinal Tract

The numbers of T lymphocytes present in the bowel wall are increased in inflammatory bowel disease, especially in Crohn's disease. The increase occurs primarily in the submucosa and deeper layers of the bowel wall and possibly reflects a chronic immune reaction with the diseased gut in response to a primary antigenic challenge to the bowel that may be bacterial (1). Intraepithelial lymphocytes (theliolymphocytes) are also more numerous in inflammatory bowel disease than in the normal bowel. Evidence suggests that these lymphocytes may be abnormal both structurally and functionally, as they respond better to PHA than to concanavalin A, which is the reverse of the normal response.

Also, the amount of secretory IgA appears to be decreased in the rectal epithelium of involved rectal mucosa in ulcerative proctitis and in 40% of proximal, normal-appearing sigmoid colon mucosa (33). This decrease suggests a local immune defect that may increase antigen penetration and vulnerability. Rectal biopsies of patients with both ulcerative colitis and Crohn's disease demonstrate increased numbers of IgE plasma cells. The role of these cells and the increased numbers of MAST cells in the colonic tissue of IBD patients suggests an immediate hypersensitivity response. Clinical trials of cromolyn sodium, as discussed below, have been held to study this response (48).

In summary, patients with inflammatory bowel disease have decreased numbers of T cells (and decreased PHA and antigen stimulation) as well as increased numbers of B cells (25-34). The significance of the pathophysiological role of decreased suppressor cell activity is unclear at the present time (27). Further uncertainty also arises because none of the above laboratory variables has any direct correlation with disease site, duration, activity, therapy, or malnutrition. An exception are those patients with high levels of immune complexes (34).

Whether these changes are primary (hence causal) or secondary (epiphenomenon) is not clear at the present time. Perhaps the initiating event is an infectious process that causes mucosal damage and loss of suppressor T cells with increased mucosal absorption of bacterial antigens. In this way, inflammation could persist and the disease would become chronic. The level of penetration of these antigens could determine if ulcerative colitis at the mucosal level or Crohn's disease at the level of the submucosa and deeper would occur. The alternate complement pathway may also be activated by endotoxin from gram-negative bacteria (35).

Therapeutic Considerations

Ulcerative colitis

Sulfasalazine has been used successfully for many years in ulcerative colitis. The drug consists of 5-aminosalicylic acid and sulfapyridine linked with an azo bond. Reduction via

cleavage at the azo linkage occurs in the 70% of the drug that reaches the colon, and the absorbed sulfapyridine is metabolized and excreted. Although only minimal amounts of the 5-aminosalicylic acid are absorbed, it has been shown to be helpful clinically when applied locally. Several effects on polymorphonuclear function can be demonstrated, such as decreased migration, superoxide production, and myeloperoxidase-mediated iodination and cytotoxicity. Inhibition of fecal prostaglandin levels probably reflects only reduced inflammation and granulocyte accumulation that does not occur via a direct synthetic inhibitory effect (24).

Bean in 1962 (36) first reported the beneficial effect from the use of 6MP, and the University of Chicago in 1966 reported that eight of 10 cases improved with azathioprine, although the dose was high (4-6 mg/kg/day for 2-3 weeks and then 2-3 mg/kg/day) (37). However, it was not until 1972 that the first controlled trial was published that showed that 11 of 20 patients on azathioprine were free of symptoms for one year versus 5 of 20 patients on a placebo (38). Although the long-term benefit was less clear (39), many studies showed some benefit especially in allowing a reduction in the steroid dosage.

In all, many drugs have been tried, including chlorambucil and busulfan as well as nitrogen mustard (mechorethamine), but there appears little justification for their use since the disease can be cured by colectomy.

Crohn's disease

In Crohn's disease, drug therapy can be better justified since the disease has no known cure, but even here no treatment has been shown to be helpful in reducing postoperative recurrences, which are as high as 30-60% (40).

The first trial of azathioprine was reported in 1969 (41), with six treated patients showing improvement over a six-month follow-up period. In the uncontrolled trials that followed, steroid requirements decreased and fistulae were healed. Between 1974 and 1978, there were seven randomized, controlled trials using 6MP or azathioprine (42). One study by Willoughby (43) of 22 patients in a 24-week, double-blind trial showed that 10 of 11 patients on azathioprine remained in remission for 24 weeks versus 8 of 11 placebo patients who relapsed.

A time period of at least four months may be needed to show the benefit, as other studies (44-45) have suggested that a peak response occurs only after three to nine months. A recent trial showed that 32% of patients did not benefit from 6MP and steroids for at least three months and that 19% benefited after four months.

In another study (46), metronidazole, which is antibacterial to some anerobes, used in a dose of 20-40 mg/kg/day produced good clinical improvement in 13 of 17 treated patients. Other studies could not confirm these results, although Crohn's disease may possibly have improved through the antibacterial action (47) of the drug.

Cromolyn sodium has also been used in a double-blind, crossover trial in doses of up to 2 gm per day per month (48). Twelve patients were significantly improved in their sense of well-being, sigmoidoscopic appearance, histology, and total eosinophil count reduction over a six-month trial period (48). Heatley, et al (49) reported that in their study there was a good response to combined oral and topical cromolyn in chronic proctitis, especially where the total eosinophil count in the lamina propria was high. Willoughby, et al (50) compared disodium cromoglycate to salazopyrine in maintaining remission in 120 patients with ulcerative colitis. On cromoloyn alone there was a 44% relapse rate (the same as placebo) versus a 12% relapse rate on salazopyrine. They could not demonstrate a good prognostic effect from the number of lamina propria eosinophils and felt that Heatley's good results reflected the use of cromolyn as a topical retention enema (50).

Three trials of BCG with various techniques have been published. In an uncontrolled trial (51), Geffroy suggested improvement in Crohn's disease when BCG was administered by scarification, while Dupuy's study failed to show any benefit (52). Using oral BCG, Rahban in nine cases (53) failed to show any changes in x-ray, clinical parameters, or laboratory values. Although the five patients who were initially DNCB-negative became positive, no improvement was seen.

A double-blind, controlled trial of transfer factor from "healthy" relatives of patients with Crohn's disease failed to produce any benefit, and no changes in T or B cell function were seen, although there was a trend to converting the negative delayed hypersensitivity skin tests to positive (54).

Although treatment of Crohn's disease with drugs like the corticosteroids helps in controlling acute relapses, no agent has as yet been shown that will alter the natural history and prevent relapses. It would seem that this goal must await a more complete understanding of the specific pathophysiology involved in inflammatory bowel disease.

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