MANAGEMENT OF INFLAMMATORY BOWEL DISEASE

ESSAY

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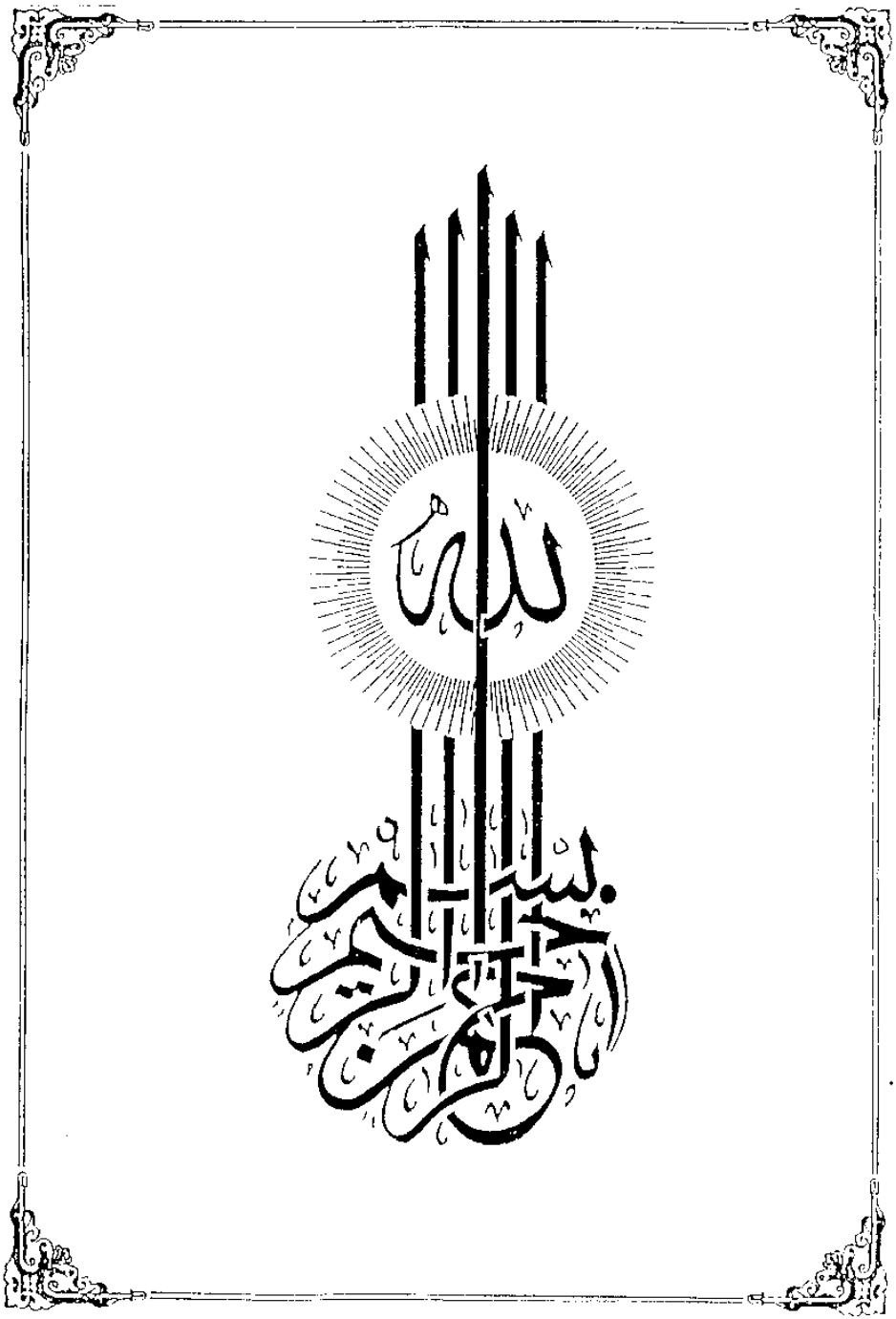

CONTENTS

Introduction

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Inflammatory bowel disease is a generic term that refers to idiopathic chronic inflammatory disease of the intestine, primarily ulcerative colitis and Crohn's disease. Ulcerative colitis, as the name implies, is an inflammatory ulcerative process of the colon. Crohn's disease is a transmural granulomatous enteritis that may involve any part of the intestine, but primarily distal small intestine and colon (*Rosenberg*, 1985).

These two conditions of unknown etiology share a number of clinical and immunologic and genetic features including extra-intestinal complications and response to treatment. Therefore, they are considered together despite distinguishing and pathological features (*Rosenberg*, 1985).

Historical Review

Crohn's diseases was discovered in 1932, yet soon after Crohn's separation, of what he initially called "terminal ileitis" from other chronic inflammatory diseases of the small intestine. It was recognized that the disease, though most frequent in the terminal ileum, may affect any

segment of the intestine and, hence, the term "regional enteritis" was used for many years thereafter. It was unclear whether the disease could also involve the colon, but for the past 20 years colonic involvement has been universally recognized. Moreover, it is now accepted that the disease may involve any portion of the gastrointestinal tract, from mouth to anus (*Storer,* 1984).

Goligher and his colleagues have traced the evolution of surgical approaches to ulcerative colitis in an authoritative manner. Sigmoid colostomy, curiously enough, was the first well-documented surgical procedure for inflammatory bowel disease (*Pennel,* 1850). During the remainder of the nineteenth century, a variety of diverting procedures were accomplished, but without success. Appendicostomy, first performed in 1902 for ulcerative colitis, represented a major advance. It soon was displaced by a completely diverting ileostomy (1913), which was accompanied by piecemeal resection of the diseased colon over the ensuing 40 years. A single-stage ileostomy, with subtotal colectomy or total coloproctectomy has emerged. Yet recently ileoanal anastomosis followed by ileoanal anastomosis with pouch (*Goligher et al.,* 1968).

Pathology and Etiology of Ulcerative Colitis

PATHOLOGY AND ETIOLOGY OF ULCERATIVE COLITIS

A. Definition

Ulcerative colitis may be defined as an acute, subacute or chronic inflammation of the colon and rectum (proctocolitis) of unknown etiology of pathogenesis. It has the following features:

1. A variable course, unpredictable prognosis and many local and systemic complications.
2. Rectal bleeding, diarrhea, cramping, abdominal pain, fever, anorexia and weight loss.
3. Proctosigmoidoscopic and roentgen features that are usually diagnostic.

It is predominantly a diffuse mucosal disease with continuous involvement without skip areas and is characterized pathologically by crypt abscess, ulcerations, increased capillary formation and vascular congestion (*Farmer et al.,* 1985).

B. Etiology

Ulcerative colitis is still idiopathic despite many years of study and voluminous publications by persons of diverse interests and backgrounds. Ulcerative colitis-like lesions of the cecum and colon have been induced in small laboratory animals by the feeding of carrageenan, a hydro colloid extracted from seaweed which is widely used as a food additive. Pretreatment of carrageenan recipients with metronidazole, an antibacterial primarily active against anaerobic bacteria, prevents colitis in the majority of animals, suggesting that anaerobic bacteria play a role in the initial events of carrageenan-induced colitis. This is a convenient laboratory model but unfortunately appears to have little or no relationship to the human disease (*Storer et al.*, 1984).

The similarity of the clinical picture in idiopathic ulcerative colitis to that of the specific dysenteries has led to attempts to implicate specific microorganisms. There are a few documented cases of chronic ulcerative colitis following proved "shigella" or amebic dysentery, but such cases are the exception and not the rule. Specific therapy directed against shigella or E. histolytica rarely exerts any beneficial effect on the course of the ulcerative colitis. Furthermore, the incidence of ulcerative colitis is low where these specific dysentery infections are endemic. Other

organisms that have been proposed as specific etiologic agents include an enteric diplostreptococcus and Bacterium necrophorum. New evidence for a transmissible infectious factor has been presented by *Cave and associates* (1980) who injected filtered homogenates of ulcerative colitis tissues into rabbits and produced histologic changes in the rabbit colon that resemble those in the human disease. These data suggest a virus but do not rule out L forms of mycoplasmas (*Bartlett,* 1981).

The generally favorable influence of adrenal corticosteroids on the course of chronic ulcerative colitis has led to a revival of the thesis that allergy or hypersensitivity plays a role in the genesis of the disease. Occasionally patients have a remarkable remission of symptoms following omission of milk and milk products from their diets. Antibodies to cow's milk proteins can be demonstrated in some patients with ulcerative colitis, and it has been suggested that this may be attributable to early weaning with ingestion of cow's milk formula before fourteen days of age. This exposes the infant to foreign proteins at a time of immunologic tolerance and permissive absorption of whole proteins. But circulating antibodies to cow's milk protein can be found in control patients with the same frequency as in patients with ulcerative colitis. Furthermore, circulating antibodies to milk proteins are not correlated with the presence or absence of clinical intolerance to milk. The

occasional intolerance to milk may be related to a secondary deficiency in intestinal lactase rather than to a specific allergy (*Storer et al.,* 1984).

Shorter and associates (1968) have proposed that the inflammatory bowel diseases are produced by local hypersensitivity reactions. Initial sensitization of the gut-associated lymphoid tissues is thought to occur in the neonatal period before the mucosal barrier is complete, permitting penetration of enterobacteria and macromolecules. Re-exposure to bacteria and intestinal antigens may occur in later life if the mucosal integrity is damaged by infection, ischemia, or even metabolic alterations induced by emotional stress. Antigen re-exposure then causes the local primary cellular immune-mediated hypersensitivity reaction, with the production of inflammatory bowel disease (*Shorter et al.,* 1968).

Hemorrhagic colitis, somewhat resembling the human disease, has been produced in several different laboratory animals by the administration of anticolonic antisera. These experimental immune lesions of the colon do not completely reproduce human ulcerative colitis, and their occurrence does not necessarily imply any correlation with the natural genesis of human ulcerative colitis. They demonstrate only that the colon can generate autoimmune reactions. Immunosuppressive drugs, particularly azathioprine, might be expected to exert a beneficial effect if

ulcerative colitis is truly an autoimmune disease. The results to date are inconclusive: some but not all patients are improved, and the benefit is slower and less marked than with corticosteroids (*Hibi et al.,* 1982).

Studies indicate that sensitized lymphocyte play an important role in autoimmunity in ulcerative colitis and suggest that a more fruitful approach would be via the cellular factors of hypersensitivity rather than circulating antibodies. It has been clearly demonstrated that circulating lymphocytes, but not sera, from patients with ulcerative colitis are cytotoxic for human fetal or adult colon epithelial cells. Lymphocytes from normal control are not cytotoxic (*Storer et al.,* 1984).

Prostaglandins, widely involved as mediators of the inflammatory process, have come under suspicion in ulcerative colitis. The production of prostaglandins in colonic mucosa has been found to be enhanced in ulcerative colitis and to be inhibited by steroids and sulfasalazine. Evidence to date implicating prostanoids is preliminary and only suggestive, however (*Storer et al.,* 1984).

Similarly, clostridium difficile toxin, the presumed mechanisms of antibiotic-associated pseudomembranous colitis, has been suggested as a contributing factor to mucosal injury in inflammatory bowel disease. But current evidence indicates that C. difficile toxin appears only in patients

exposed to antimicrobials and play no important etiological role in IBD (*Bartlett,* 1981).

Numerous attempts to implicate mental disorders in the etiology of ulcerative colitis have produced no convincing evidence. Patients with psychoses or depressive reactions are not prone to develop ulcerative colitis, nor has functional bowel distress been observed to lead to ulcerative colitis. Whereas it is certainly true that ulcerative colitis patients manifest abnormalities of the psyche, such abnormalities may well be the effect, not the cause, of the disease – a somatopsychic rather than a psychosomatic disorder. *Esler and Goulston* (1984) have assessed the levels of anxiety and neuroticism in patients with ulcerative colitis and in general medical patients; there was no significant difference in these dimensions of personality. *Mendeloff and associates* (1984) compared life stresses in patients with ulcerative colitis and control subjects drawn from the same population group. They concluded that "this and other studies fail to support the thesis that ulcerative colitis is a paradigm of psychosomatic illness."

The search for a single cause of ulcerative colitis may be unrealistic. The colon can respond to injury (in the broad sense) in a limited number of ways. Several etiologic factors may have in common

the initial injury to colonic mucosa in biologically predisposed individuals. Perpetuation of the process could well be due to a different mechanism(s) (*Storer et al.*, 1984).

Gross Pathologic Appearances of Ulcerative Colitis

Ulcerative colitis virtually always involves the rectum to produce proctitis although steroid enemas may mask this distribution (*Price*, 1977).

The more proximal regions of the colon are variably involved to produce proctosigmoiditis or proctocolitis. The pathological findings in ulcerative colitis depend upon the severity, the clinical phase and duration of the disease (*Marson and Dawson*, 1979). In the early phases, ulcerative colitis shows only mucosal congestion, with active chronic disease, the mucosa becomes granular, velvety and friable with superficial erosions, such that the mucosa can be wiped off. As the disease continues, the involved area lose their haustra and become flat.

When ulceration occurs in ulcerative colitis, the ulcers are usually in the midst of grossly abnormal mucosa, they are usually irregular but linear longitudinal oriented ulcers that overlie the taeniae coli occur. With