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INFLAMMATORY BOWEL DISEASES

ESSAY

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BY

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Maher Nessiem Ghabriel

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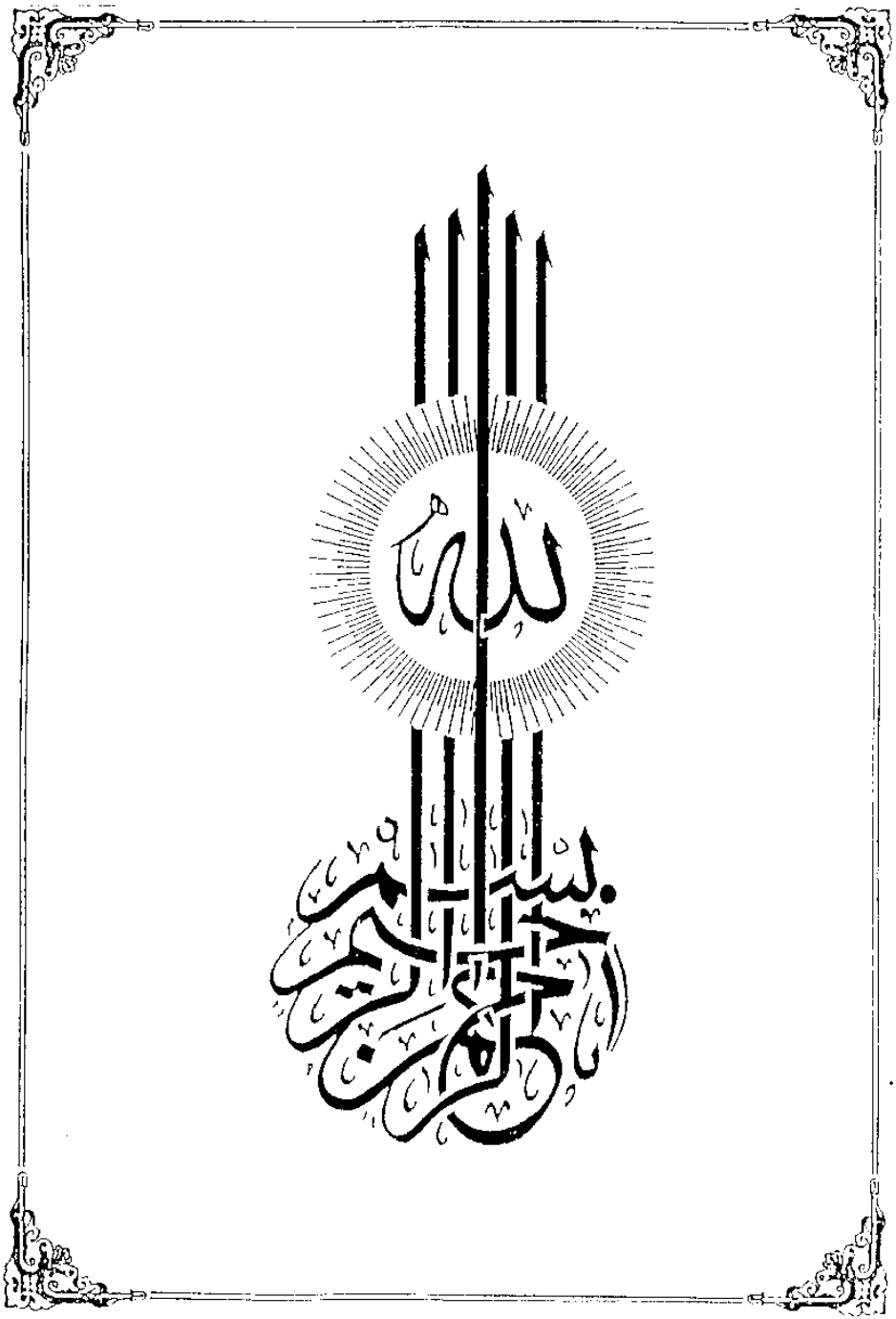

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I - INTRODUCTION

Inflammatory bowel disease is a general term designated to a number of clinicpathologic disorders in children and adults who present with similar clinical manifestations which include fever, diarrhoea - with or without blood - and distension (Kirsner, 1978). In addition to the well-known granulomatous enterocolitis - Crohn's disease (Mayberry and Rhodes, 1984), chronic ulcerative colitis (Morris and Rhodes, 1984) and those infectious enterocolitis-tuberculosis (Schwartz et al., 1984), amoebiasis (Holt, 1981), Shigellosis (Nalin, 1984) and salmonellosis (Longfield, 1984) - the diversifield list has expanded with the inclusion of neonatal necrotizing enterocolitis (Cogbill and Milliken, 1985), ischaemic enterocolitis (Demetriou et al., 1985) and antibiotic - associated bowel disease (Patterson et al., 1984).

Some points that should be stressed are that many gaps still exist in our understanding of the aetiology and pathogenesis of these diseases (Kirsner, 1978 and wormann et al., 1985). Inflammation alone is an inadequate characterization of the tissue reaction since ulceration, necrosis, vascular changes, fibrosis and atrophy are other important pathologic components regardless of the specific diagnostic terminology. These overlapping features are a constant source of potential confusion to the pathologist who examines these case, although some specific macro and microscopic findings are importantclues (microorganisms, granulomas, vasculitis, skip areas) when correlated with the appropriate clinical setting (Price and Morson, 1975). From the perspective of the surgical pathologist, it is imperative that some clinical impressions are available at the time of tissue examination (Dehner, 1979).

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The similarity of the clinical manifestations and the overlapping pathological features are a source of diagnostic error, whoever, through a careful history and physical examination, laboratory and roentgenographic studies and endoscopic visualization usually with biopsies that one can arrive at a reasonably specific interpretation (Dehner, 1979). Various clues such as age, extent of disease and anatomic localization are important in the differential diagnosis (Dehner, 1979).

This review will discuss the aetiology, pathogenesis, clinical manifestations, complications, diagnosis, medical and surgical lines of treatment and prospects of those suffering from inflamma tory bowel disease with particular emphasis on recent advances in the field of this obscure disease.

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II - ULCERATIVE COLITIS

This term denotes a form of colitis of unknown aetiology, characterized by ulceration of the mucosa. In some patient ordinarily classed as suffering from the disease no such gross ulceration is present, but the mucosa instead showing to the naked eye just a diffuse thickening and granularity - though it is microscopically ulcerated. Although the rectum is involved in the great majority of cases, sometimes being the part of the large bowel mainly solely affected (Goligher et al, 1984).

Epidemiology

Age and Sex Incidence

The respective epidemiologies demonstrate that children and young adults are the usual victims but the age extremes are not spared (Farmer et al., 1975, and Ament, 1975). The data provided by Watts et al., (1966 c,d) showed that roughly half the patients were between 20 and 39 years of age at the commencement of their colitis, and that at all ages females preponderated over males in the ratio of about 4 : 3. It is interesting to note however that in the series of cases of colitis commencing in childhood reported by Ross, (1964) and Canby and Mehlhop, (1964) there was a reversal of the sex ratio. Morris and Rhodes, (1984) have examined the incidence of ulcerative colitis in the Cardiff region during the decade 1968 - 1977. In South Glamorgan, ulcerative colitis was very rare in childhood but the incidence rose steeply to reach the first peak in early adult life. The slight decline in incidence in middle life was almost confined to women but both sexes showed a second peak of incidence in old age. Indeed the highest incidence of ulcerative colitis in Morris and Rhodes, (1984) study was in

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70-79 years age group (15.1/10^5). They could not offer an explanation for such age distribution.

Geographical Incidence

Melrose, (1955,1956) studied the incidence of colitis in different parts of Britain and the Continent of Europe. His findings showed that colitis appeared to be twice as common in England as in Scotland or certain other European countries. Carleson et al., (1962) And Chojecki, (1963) estimated the frequency of colitis in Sweden and Poland as 3.5 and 6.6 respectively per 10.000 hospital admissions. Gjone and Myren, (1964) reported the incidence of ulcerative colitis in Norway rose from 8.6 per million during 1951-1956 to 20.6 per million between 1956 and 1960. The corresponding annual rate of incidence of the disease in New-Zealand during 1954-58 was given as 50-60 per million of population (Wigley and Mclaurin, 1962). The mean incidence of ulcerative colitis in South Glamorgan between 1968 and 1977 was 7.2 ± 1.5/10^5/year (Morris and Rhodes, 1984). Studies from various centers suggest that the incidence of ulcerative colitis was rising before 1960 but has been steady over the last 20 years. Recent studies from the United Kingdom are exceptional and show a very high rising incidence of ulcerative colitis so no overall pattern has emerged (Morris and Rhodes, 1984).

Constitutional factors :

Race

In NewZealand Wigley and Maclaurin, (1962) found that colitis was much more prevalent among the population of European stock than among the Maoris. The disease also appears to be rarer among Negroes than white people in United States of America (Monk et al., 1967), and may also be rarer in American Indians (Behchuk et al., 1961).

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Acheson and Nefzger, (1963) proved that colitis is two to three times as frequent amongst Jews and among non-Jewish. It is interesting to note, however, that amongst Jews in Israel considerable difference in the prevalence of colitis occur according to their ethnic origin (Birnbaum et el., 1960).

Social Status

In Acheson and Nefzger's (1963) study of the United States Army personnel, it was found that colitis was commoner among officers than among enlisted men, and among former salemen than among former agricultural workers. The greater frequency of colitis in urban than country dwellers was also pointed out by Wigley and Maclaurin (1962) in New Zealand.

Blood Groups

In two studies by Boyd et al., (1961) and Maur et al., (1964) it was confirmed that there is no correlation between the incidence of colitis and the ABO and MN blood groups or secretor status, but apositive correlation was found with Rhesus type CC (Boyd et al., 1961 and Thayer and Bore 1965).

Familial Occurence

The familial incidence of ulcerative colitis was stressed by Barker, (1962); Kirsner and Spencer, (1963) and Gloligher et al., (1968). All have provided support for this concept. On the basis of their findings therefore, it seems justifiable to assert that there is a genuine familial predisposition to colitis. It is important to remember, however, that at least 90 percent of the patients have no familial history of the disease.

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Non-smoking a feature of ulcerative colitis patient

Harries et al., (1982) were unable to provide any explanation for the results of their study on smoking and inflammatory bowel disease which showed significantly lesser indulgence in smoking in persons with colitis. This result has been confirmed by further studies (Bures et al.,1982; Jick and Walkder, 1983 and Logan et al., 1983). The relevance of this finding is at present not clear (Bailas, 1983), but it has been suggested that smoking may protect against ulcerative colitis. Holdstock, (1984) confirmed the low prevalence of smoking among patients with ulcerative colitis, but smokers tended to do worse on most counts. Two explanations are possible, either smoking has a direct effect on the disease or patients who have more severe symptoms find psychological relief by continuing smoking. In either event, these findings together with the known health hazards of smoking lead the author to conclude that, for the present, patients with inflammatory bowel disease should be advised to stop smoking (Holdstock, 1984).

Aetiology

The actiology of ulcerative colitis remains unknown. Many theories have been proposed including infective, autoimmune, dietary, and psychosomatic. None of them has proved generally applicable and we are still almost totally ignorant of the cause of this disease. Only a bare outline of these aetiological factors will be attempted.

Lysosome and Mucinases

Lysosomes have been implicated in the pathogenesis of ulcerative colitis in man (Danovitch et al., 1972). Morain et al., (1984) noted decreased activities of lysosomal enzymes β- glucuronidase, acid phosphatase and

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N- acetyl- β- glucosaminidase, in ulerative colitis, particularly in active disease. Danovitch et al., (1972) have found decreased concentrations of aryl sulphatases and β- glucusonidase, but surprisingly, increased concentrations of acid phosphates in tissue homogenates from patients with ulcerative colitis. Clearly further studies are necessary to investigate the role of lysosomal enzymes in the pathogenesis of inflammatory bowel disease.

Infection

Infection with suppuration and destruction of tissue probably plays a part in producing some of pathological changes found in ulcerative colitis, but so far as we know this is due entirely to organisms ordinarily resident in the colon and filling the role of secondary invaders (Goligher et al.,1984). Brooke, (1954), have suggested that damage to the colon by preceding attack of dysentery, bacillary or amoebic, may often be the factor that initiates ulcerative colotis. But the vast majority of cases of colitis met in practice have clearly had no previous attack of dysentery (Goligher et al., 1984).

Unlike earlier reports of La Mont and TRnka, (1980) and Trnka and La Mont,(1981); Grenfield et al's(1983) prospective study does not show a relationship between the clinical assessment of inflammatory bowel disease activity and the presence of clostridium difficile in the stool. They proved that there is no causal relationship between cl. difficile's presence and disease activity.

An aetiologic role of campylobacter species in inflammatory bowel disease has not been comprehensively sought, but the literature contains reports of campylocacter infection resembling exacerbation or actue presentations of inflammatory bowel disease (Martin et al.,1984). He concluded

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that the available data do not implicate campylobacter as either an aetiologic agent or a common cause of exacerbations in inflammatory bowel disease.

Viral agents have been implicated both in the cause and in the perpetuation of inflammatory bowel disease. Rota virus, Norwalk virus and a newly described serologically distinct group of adenoviruses also appear to be able to produce acute enteritis (Blocklow and Cukor, 1981). In addition to the possibility that viruses may cause inflammatory bowel disease, it has been suggested that intercurrent acute viral inflections may play a role in the progress or exacerbations of these diseases (Mee and Jewell, 1978). While Yoshimura et al., (1984) provided no evidence in support of a viral association with or aetiology for inflammatory bowel disease, it does not preclude those possibilities. Viruses may be involved in the pathogenesis of inflammatory bowel disease, but these agents may be undetectable by current standard tissue culture techniques. Alternatively, viruses may be necessary only at the initial stage of infection and may be unnecessary at least in conventional infectious forms, for further development of the disease, which might be produced by autoimmune mechanisms. Most recently Wormann et al., (1985) reported a case of relapsing ulcerative oesophagitis presumably due to herpes virus infection in temporary association with two relapses of an idiopathic inflammatory bowel disease and the authors stressed the need to search for signs of viral infections in relapses of idiopathic inflammatory bowel disease.

Psychological Influences

It is generally stated that patients with ulcerative colitis are often highly strung and introspective and their attacks frequently coincide with periods of increase stress (Groen and Van der Valk, 1956). Though Paulley,

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(1971) has claimed dramatic, almost invariable clinical improvement in patients with ulcerative colitis by means of psychotherapy, most clinicians find the results of psychological treatment less consistent. Goligher et al., (1968) proved that 86 percent of their patients seemed to be normal, well adjusted individuals whose emotional make-up did not obviously differ from that of the population at large. It is noteworthy that after surgical treatment, even the colitis patients exhibiling some psychopathic stigmata preoperatively soon lose them, suggesting that they are probably an effect rather than cause of the disease.

Immunological factors

The most popular theory at the moment is that ulcerative colitis represents an immunological response to antigens, which may be alimentary (food, chemicals or drugs), bacterial or autogenous.

Alimentary Antigens

Andersen, (1942) first focused attention on this possibility of describing a case of ulcerative colitis due to food allergy. He was able to report that the responsible allergen in the majority of these ulcerative colitis patients was milK, and rarely other foods. Despite this suggestive evidence, the theory that ulcerative colitis represents an immunological reaction to certain foods has still to be proved, for it is yet to be shown that with holding of certain food substances can cure all patiens of their disease (Goligher et al., 1984).

Autogenous Antigens

It is possible that ulcerative colitis may be an autoimmune disease. Broberger and perlmann, (1959) were able to demonestrate circulating anti-

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bodies to human fetal colon, liver and kidney in the sera of children with ulcerative colitis. These antibodies were not present in the sera of normal healthy subjects. However, it is possible that these positive findings represented serological reactions to bacterial antigens. Broberger, (1964) himself subsequently sounded a note of caution in regard to the acceptance of an autoimmune process as the main aetiological factor in ulcerative colitis.

PATHOGENESIS

Immunological Mechanisms and Inflammatory Bowel Disease

The pathogensis of inflammatory bowel disease is unknown. Immunological mechanisms, however, both humoral and cell mediated mechanisms may be involved (Thomas and Jewell, 1979). In particular defective suppressor cell function has been found in the peripheral blood of patients with inflammatory bowel disease (Victorino and Hodgson, 1981).

Selby and Jewell, (1983) studies peripheral blood T lymphocytes and T lymphocyte subsets in inflammatory bowel disease patients. The results of their study indicated that the pathogenesis of ulcerative colitis does not depend upon an alteration in the proportion of circulating T lymphocytes nor upon an imbalance of T lymphocyte subsets as defined by monoclonal antibodies. Their results also showed reduction in T lymphocyte numbers in peripheral blood which may result from mucosal infiltration which has been demonstrated in patients with active inflammatory bowel disease (Meuwissen et al., 1976). It is possible that within the intestinal mucosa there may be abnormal numbers or a redistribution of T lymphocyte subsets

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or an alteration in the mucosal microenvironment which may be important in the pathogensis of inflammatory bowel disease (Selby and Jewell, 1983). The results of Selby et al., (1984) showed that in inflammatory bowel disease there is infiltration of the mucosa with lymphocytes, both T cells and B cells. The proportions of T lymphocyte subsets, as defined by monoclonal antibodies, do not differ, either in the epithelium or in the lamina propria, from those seen in normal colonic mucosa. This is true in inflammatory bowel disease regardless of disease activity or mode of treatment. These mucosal populations are also similar to those seen in normal small intestine (Seilby et al., 1984). The findings indicate that the pathogensis of inflammatory bowel disease does not depend upon an imballance of the immunoregulatory T cells defined by the monocional antibodies (Selby et al.,1984).

Against Selby et al.,'s (1984) results Godin et al.,'s (1984) date which indicated that patients with active inflammatory bowel disease, untreated by steroids, have significant decrease in both the absolute numbers and relattive proportions of their suppressor T cells. This decrease was sufficient in ulcerative colitis patients, to be reflected by a significant decrease in total lymphocyte count. This decrease in suppressor cells also resulted in consistant rises in the relative proportions of helper T. cells and consequently in raised helper suppressor ratios. These rises in ratios tended to be coincide with periods of clinical exacerbation of disease. No alterations in absolute numbers or proportions of helper or suppressor cells were noted in steroid treated patients, patients with inactive disease or patients with other gastrointestinal or liver disease (Godin et al., 1984).

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