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Historical origins of current IBD concepts

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INTRODUCTION

The "nonspecific" inflammatory bowel diseases, ulcerative colitis and Crohn's disease, represent a group of heterogeneous inflammatory and ulcerative diseases of the small and large intestines of unknown etiology, associated with many gastrointestinal and systemic complications. Appearing initially as isolated cases in Great Britain and northern Europe during the 19th and early 20th centuries, they have steadily increased numerically and geographically and today are recognized worldwide.

ULCERATIVE COLITIS

Matthew Baillie's 1793 *Morbid Anatomy of Some of the Most Important Parts of the Human Body* strongly suggests that patients were dying from ulcerative colitis during the latter part of the 18th century[1]. The first "impact" description of "ulcerative colitis" by Samuel wilks[2] of London in 1859 concerned a 42 year old woman who died after several months of diarrhea and fever. Autopsy demonstrated a transmural ulcerative inflammation of the colon and terminal ileum, originally designated as "simple ulcerative colitis", but a century later identified as Crohn's disease[3]. The 1875 case report of Wilks and Moxon[4] describing ulceration and inflammation of the entire colon in a young woman who had succumbed to severe bloody diarrhea was an early instance of ulcerative colitis.

In 1902 R.F. Weir[5] performed an appendicostomy in a patient with ulcerative colitis to facilitate colonic irrigation with potassium permanganate for a presumed infection. J. P. Lockhart-Mummery[6] of London in 1907, aided by the then new electrically illuminated proctosigmoidoscope, discovered carcinoma of the colon in seven of 36 patients with ulcerative colitis. By 1909, 317 patients had been admitted to seven London hospitals with an inflammatory and ulcerative disease of the colon[7]. Many had died from perforation of the colon, peritonitis, hemorrhage, sepsis and pulmonary embolism. Into the 20th century similar instances of "ulcerative colitis" were being reported in Europe and in the United States. Etiologic speculation included food and pollen allergy and a psychogenic disorder. Treatment later with sulfonamides (1938) and then antibiotics, beginning with penicillin (1946), re-emphasized the possibility of a bacterial infection. The favorable responses to ACTH and adrenal steroids during the 1950s[8] stimulated interest in immunological mechanisms as discussed later.

Pathology Initial pathologic descriptions of ulcerative colitis recognized the diffuse mucosal/submucosal involvement, beginning in the rectum and rectosigmoid, and advancing proximally to involve the entire colon in a diffuse inflammation of the mucous membrane with chronic inflammatory cells, lymphocytes, plasma cells, and eosinophiles, vascular congestion, goblet cell depletion, and crypt abscesses [9]. In 1933 Buie and Bargen[10] implicated vascular "thrombotic phenomena" as the patholgical basis for ulcerative colitis and in 1954 S. Warren and S. Sommers[11] described an inflammatory necrosis of arteries, veins, or both, leading to vascular occlusions and infarction of the colon in some patients with ulcerative colitis. A 1949 review implicated an etiologic agent in the fecal stream[12], as had been proposed by P. Manson-Bahr in 1943 and earlier by B.Dawson[13] in 1909.

"Natural" and experimental colitis Veterinarians long had been aware of inflammatory diseases of the small intestine and colon in animals (dogs, cat, horse, cattle, sheep, swine, rodents), attributable to bacteria, parasites, or viruses. However, despite morphologic similarities, none duplicated human IBD. Only the colitis in cotton top tamarins (saguinus oedipus) from colombia, housed in the United States, resembled human ulcerative colitis in its clinical and histologic features and response to sulfasalazine.

Many attempts to reproduce ulcerative colitis in animals (rabbit, guinea pig, hamster, dogs, mice, rats) during the 1920s-1960s[14] included nutritional depletion (vitamin A, pantothenic acid, pyridoxine), the local application of Shiga and staphylococcal toxins to colonic explants, the vasoconstriction induced by adrenalin

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intraperitoneally in dogs, the intravenous injection of staphylococcus toxin in rabbits, enzymes (collagenase, lysozyme) intrarectally and intraarterially and carrageenan orally[15]. Topically (colonic) applied compounds (4%-10%) acetic acid, trinitrobenzene sulfonic acid in 50% alcohol), orally administered drugs (indomethacin, mitomycin-c), and inhibition of fatty acid oxidation[16] caused temporary colonic injury.

CROHN'S DISEASE

In 1612 Gullielmus Fabricius Hildenus (Wilhelm Fabry)[17] (1560-1634) noted at autopsy in a boy who had died after persistent "abdominal pain" and diarrhea that "the ulcerated cecum (was) contracted and invaginated into the ileum". G.B. Morgagni[18] (1682-1771) in his 1769 "De Sedibus et Causis Morborum" described ulceration and perforation of an inflamed distal ileum and enlarged mesenteric lymph nodes in a young man of 20 with a history of diarrhea and fever culminating in death after 14 days. Similar cases were reported by Combe and Saunders[19] and by Abercrombie[20]. Abraham Colles[21] of Dublin in 1830 described Crohn's disease among children and the complicating perianal, rectovaginal and rectovesical fistulas. In 1889 Samuel Fenwick[22], in a 27 year old woman with a history of diarrhea and weight loss, at autopsy observed "adherent loops of intestine with a communication between the cecum and adherent small intestine…" The lower end of the ileum was dilated and hypertrophied and the ileocecal valve was contracted to the size of a swan's quill. Early in the 20th century, case reports from Europe documented the occurrence of a similar condition associated with lower abdominal (inflammatory) masses, assumed to be "malignant" and, at a time of limited abdominal surgery, arbitrarily dismissed as "untreatable"[23].

The classic 1913 paper by T.Kennedy Dalziel[24], including 13 patients, antedated Crohn's contribution by nearly 20 years. The first patient had experienced bouts of cramping abdominal pain and diarrhea since 1901, progressing to intestinal obstruction and death. At autopsy, the entire small intestine was chronically inflamed and the mesenteric lymph nodes were enlarged. Dalziel attributed his "chronic interstitial ileitis" to Johne's mycobacterial intestinal disease of cattle.

By 1920 American physicians were reporting instances of hyperplastic, granulomatous lesions of the intestinal tract, originally identified as "hyperplastic intestinal tuberculosis." The clinical features were similar: young patients (children, teenagers, and young adults) often operated upon for "appendicitis", symptoms of fever, abdominal cramps, diarrhea, and weight loss. The disease usually involved the terminal ileum or ileocecal area. In a 20 year old man, three bowel resections were required within 18 months for recurrent intestinal obstruction[25]. In some countries (United States, England, Sweden) but not in others (Denmark, Norway), Crohn's disease was more commonly reported among Jewish people (Ashkenazi rather than Sephardic) regardless of native birth, immigrant history or orthodoxy.

Immediately preceding the paper by Crohn *et al*[26] in 1932, F.J. Nuboer[27] of Holland and M. Golob [28] of New York (1932) and in 1934 A. D.Bissell[29] of the University of Chicago reported instances of a similar disease. In 1936 Crohn *et al*[30] described 9 patients with combined ileitis and right-sided colitis. Fone[31] of Australia, noted that 40 of 41 patients had had at least one abdominal operation. Despite early European and American descriptions of colonic involvement by Crohn's-like inflammatory lesions[32, 33], the concept was not completely accepted in America until the 1959 and 1960 reports of Lockhart-Mummery *et al*[34,35].

Etiologic speculation included bacteria, viruses, abdominal trauma and impaired vascular and lymphatic circulation. In 1943, Tallroth[36], noting many eosinophils in histologic sections, termed the disease "ileitis allergica". The concept of an endolymphangitis provided the rationale for the 1936 experiments of Reichert and Mathes[37] who injected fine sand and the sclerosing solution of 26% bismuth oxychloride with Esch. Coli into the cannulated mesenteric lymphatics of dogs, producing an edema of the ileocecal area. Chess [38] in 1950 fed dogs silica and talc; and kalima *et al*[39] (1976) injected formalin solution into the mesenteric lymphatics, producing an endolymphangitis but not regional enteritis. Van Patter *et al*[40] in 1954 suggested that "the causative agent may be found in the fecal stream" entering the lymphatic system and causing lymphatic obstruction, dilatation and lymphoid hyperplasia but this possibility again went unnoticed.

Pathology of Crohn's disease In 1938 Coffey[41] emphasized the subacute or chronic, granulomatous inflammatory process, the tendency to intestinal stenosis and the fistula formation. In 1939 G. Hadfield[42] of England noted thickening of the ileum, fistulas from bowel to abdominal wall and to the urinary bladder, the giant-cell systems in the submucosa and in regional lymph nodes and the lymphedema of the submucosa. Warren *et al*[43] described the process as: "A progressive sclerosing granulomatous lymphangitis, probably a reaction to an irritative lipid substance in the bowel content." Rappaport's[44] 1951 study of 100 cases included 85

bowel resections and 15 autopsies; in 72 instances, sections from mesenteric lymph nodes, and in 35 appendices, documenting the gross features of Crohn's disease: adherent mesentery, thickened distal small bowel, enteric fistulas, intestinal narrowing, aphthous and linear serpiginous ulcers, a cobblestone appearing mucosa, and an asymmetrical distribution of disease. The tiny slit-like ulcer, located precisely over the M cell in the epithelium overlying lymphoid follicles in Peyer's patches[45], the granulomas, the focal distribution and the lymphoid prominence conveyed as "pathogenetic" histologic features of Crohn's disease.

EPIDEMIOLOGY

An epidemiological approach to inflammatory bowel disease was not feasible until the 1950s. Melrose [46] in 1955 collected information on 1425 patients with chronic idiopathic ulcerative colitis for the years 1946 to 1950 and proposed an incidence of 10.9% per 10 000 general admissions. The rate of 6.9% for the five Scottish towns in contrast to 15. 5% for the London hospitals was early recognition of the urban: rural IBD incidence differential. Houghton *et al*[47] in 1958, on the basis of 170 patients with ulcerative colitis and 32 with ileitis in Bristol, England for 1953, 1954, and 1955, estimated annual incidence rates of 0.85 per 1000 for ulcerative colitis and 0.14 per 1000 for regional ileitis. Ustvedt[48] of Norway in 1958, for the ten year period 1945-55, noted a mean annual rate of 1.2 per 100 000 population. Acheson[49] in 1960 analyzing data for 2320 male veterans discharged from U.S. Veterans Administration hospitals with diagnoses of regional ileitis, ulcerative colitis, or nonspecific enteritis, observed a fourfold increase of Jewish patients, over a sample of all discharges. Acheson[50] also noted a twentyfold increase in the incidence of ankylosing spond ylitis among U.S. veterans with IBD.

In the first population study of 231 patients with ulcerative colitis (excluding proctitis), Iversen *et al*[51], in Copenhagen county (Denmark) for the period 1961-1966, reported a disease incidence averaging 7.3 per 100 000 per year. A population study of Crohn's disease in two counties in central Sweden for the period 1956-1967[52] revealed a mean incidence of 2. 5/100 000 for the first six years of the 12 year span and 5.0 during the second six year period, a rising trend observed subsequently in other geographic areas.

Epidemiologic studies by Mendeloff *et al*[53-55] in the Baltimore area during the 1960s documented the rising incidence of ulcerative colitis during the first half of the 20th century, exceeding Crohn's disease in a proportion of 4 to 5:1. Mendeloff characterized the IBD population as follows: ① Males and females nearly equally affected; ② patients more commonly western than oriental, much more often of northern European origin; ③ more often urban than rural dwellers; ④ more often caucasian than colored; ⑤ more common among Jews (Originating often in northern Europe and North America) than among non-Jews, but not common among Israelis; and ⑥ more common in families than expected. For the period 1960 to 1979 Calkins and Mendeloff[55], comparing their first and second analyses, noted an increase in the age adjusted rate for Crohn's disease over ulcerative colitis, for whites of both sexes and for non-white females. Subsequent epidemiologic surveys[56] documented the worldwide distribution of IBD, the initially increased and now stabilizing incidence of ulcerative colitis, the rising incidence of Crohn's disease, appearing also in formerly "lagging" countries (Brazil, South Korea) and the unexpectedly high incidence of inflammatory bowel disease (especially Crohn's disease) in such areas as the North Tees Health District of England.

The implication of foods in the etiology of Crohn's disease during the 1960s-1970s, especially concentrated sugars, margarine, and fats, never attained scientific credibility.

Smoking and IBD The relationship between ulcerative colitis and non-smoking, especially the occurrence of ulcerative colitis among former smokers, was first reported by S.M. Samuelsson[57] in a 1976 thesis (Uni versity of Upsala). Rhodes *et al*. of Cardiff, Wales[58] in a 1982 mail questionnaire confirmed the hitherto recognized infrequency of cigarette smoking in patients with ulcerative colitis and the excess of cigarette smoking in Crohn's disease: eight percent of the ulcerative colitis series were current cigarette smokers compared with 42% of the group with Crohn's disease and 44% of controls. Forty eight percent of the ulcerative colitis group had never smoked compared with 30% for Crohn's disease and 36% for controls. The negative association between ulcerative colitis and cigarette smoking, especially among ex-smokers and the reverse relationship between smoking and Crohn's disease, subsequently was reaffirmed in studies from other geographic areas. The biologically complex tobacco-ulcerative colitis relationship is not exclusive to inflammatory bowel disease and is present also in patients with Parkinson's disease[59], and Alzheimer's disease.

PSYCHOGENIC RELATIONSHIP

Scientific recognition of the physiologic responses of the body to emotional stress originated with the classic obser vations of Cabanis (1796)[60],

Pavlov[61], and Cannon[62] (early 1900s). Psychogenic factors were "formally" implicated in ulcerative colitis in the reports of Murray[63] (1930) and Sullivan[64] (1935), who had been impressed with a chronological relationship between emotional disturbances and the onset of bowel symptoms in men and women with significant emotional disturbances involving their marriage, home life and interpersonal relationships.

Psychiatric precepts during the 1930s, 1940s, and 1950s emphasized an "ulcerative colitis personality", described as "immaturity of the patient, indecisiveness, over-dependence, and inhibited interpersonal relationships," together with critical emotional events including the loss of a loved one, feelings of social rejection, and "maternal dominance". The 1947 experiments of Almy *et al*[65], demonstrating the physiological effects of emotional stress upon the normal colonic mucosa (hyperemia, vascular engorgement , increased secretion of mucus, and augmented colonic motor activity) and, more pronounced in the ulcerative colitis colon, appeared consistent with the psychogenic hypothesis.

Psychotherapy (conventional and *psycho*-analytical) was an important part of medical treatment during the 1930s-1950s. In 1954 Grace, Pinsky, and Wolff[66] reported lower operability rates, fewer serious complications, and lower mortality rates in 34 patients with ulcerative colitis treated by stress-control therapy. However, in a series of 70 patients with severe ulcerative colitis treated by psychoanalytically oriented psychotherapy for three months, no specific value was observed in preventing surgical intervention on severe recurrences. Feldman *et al*[67] found no evidence of a psychogenic causation in a controlled study of 34 patients with ulcerative colitis.

Early clinical reports implicating emotional difficulties in ulcerative colitis had originated in retrospective reviews of often incomplete hospital records and in uncontrolled clinical observations. Later controlled clinical and critical studies did not support the concept[68,69]. A. Karush *et al*[70] in 1977 summarized the prevailing psychiatric view: "We do not claim that ulcerative colitis is'caused' by unusual reactions of the mind alone, we claim only that these reactions almost always play a vital role in the interaction of the four etiological determinants, genetic endowment, constitutional vulnerability, intrapsychic processes, and the external environment." Today, the role of emotions and stress in human disease has extended to the realm of the neurosciences[71], perhaps involving neuroimmune interactions as the basis of the emotional contributions to IBD. Emotional disturbances were less emphasized in Crohn's disease. Blackburn in 1939 considered a majority of 24 patients "abnormally introspective". Grace [72] and others were impressed with the relationship between stress and the onset or relapse of Crohn's disease. On the other hand, kraft and Ardali[73] and Crockett[74] regarded the psychological difficulties as consequences of chronic, recurrent, and frustrating illness and this view predominates today.

MICROBIAL ASPECTS—ULCERATIVE COLITIS

Bacterial causes of ulcerative colitis attracted attention during the early 20th century when bacterial origins of intestinal disease were first being identified, including bacillus coli (1909), streptococci (1911), and B. Coli communis (1913). None fulfilled Koch's postulates, yet, bacterial possibilities influenced the treatment of ulcerative colitis for many years. Hurst[75] administered a "polyvalent anti-dysenteric serum" intravenously, Leusden[76] an autologous vaccine of fecal bacteria and later sulfonamides and antibiotics were used extensively.

Focal infection (e.g. dental infection) was a popular cause of disease in the United States during the 1920s and encouraged the extensive removal of teeth, gallbladders and appendices. The occurrence of ulcerative colitis in a patient following removal of an abscessed tooth encouraged J.A. Bargen[77] to pursue the problem, experimentally and clinically. In 1925, Bargen *et al*[78] reported positive cultures from the rectal ulcerations in 80% of 68% ulcerative colitis patients and the occurrence of colonic lesions in rabbits injected intravenously with broth containing diplostreptococci. Cook[79] and Mayo microbiologist Edward Rosenow, in 1931, injected rabbits with diplostr eptococci cultured from abscessed teeth of patients with active ulcerative colit is and described a "diffuse hemorrhagic infiltration" of the colon. Cook also inoculated artificial cavities created in the teeth of dogs with a diplostreptoc occus isolated from the teeth of patients with ulcerative colitis. Diarrhea developed in seven of 15 animals and colonic ulcerations were observed proctoscopically for months. Bargen then treated patients with an autologous vaccine of diplostreptococci, with limited success. Studies by M. Paulson[80] and by Mones *et al*[81] had failed to confirm the experiments of Bargen and the diplostreptococcus concept soon lost scientific credibility.

Other bacteria implicated and similarly discarded for lack of decisive evidence included: the anaerobe spherophorus necrophorus[82], bacillus Morgagni, pseudomonas aeruginosa, hemolytic and non-hemolytic Esch. Coli, and viruses (e.g. lymphopathia venereum). Serological evidence of unusual response to known viruses (influenza,

mumps, measles, herpes, Cocksackie A, B, Echo, E-B, Adenovir us) in ulcerative colitis has been negative. The occasional increased titers of cytomegalovirus (CMV) have been in malnourished, secondarily immunodeficient patients. In the 1940s, studies of a possible etiologic relationship with lymph opathia venereum[83] proved negative[84].

Bacterial viral causes—Crohn's disease The many bacteria implicated in Crohn's disease included Boeck's sarcoid , mycobacteria (Kansasii [1978], paratuberculosis), anaerobic organisms (including Eubacteria strains Me_{46}, Me_{47}, B. Vulgatus, peptostreptococcus, aerobacter aerogenes, coprococcus, bifidobacteria), Campylobacter fetus ssp. Je juni, Yersinia enterocolitica, Chlamydia trachomatis), mycobacterial variant (Mycobact-erium Linda)[85], bacterial components[86] (lipopolysaccharides, peptidoglycans, *oligo*-peptides), metabolic products (toxins, necrosins) and viral protein elements (virions, prions); none achieved etiologic status. Serological studies of Epstein Barr, Echo A, B adenovirus, rotavirus, and Norwalk virus, as in ulcerative colitis, also was negative. Today, the possible role of an antecedent exposure to measles is under investigation.

Specific infections of the terminal ileum and colon in animals have been associated with tissue changes resembling Crohn's disease, including an enterocolitis in cocker spaniels (1954), mycobacterial paratuberculosis infection of the terminal ileum in cattle (Johne's disease) (1913), a terminal ileitis in swine, and a granulomatous colitis of Boxer dogs[87]. However, none of the animal diseases duplicated Crohn's disease.

IMMUNE MECHANISMS

Edward Jenner[88] in 1801 wrote that infection can alter the body in a manner that will cause its tissues to react with increased intensity to subsequent contact with the infective agent." More than 100 years elapsed before the important role of the gastrointestinal tract in the immune homeostasis of the body was demonstrated[89]. In 1919, Besredka[90] showed that oral "immunization of rabbits protected against otherwise fatal Shiga bacillus infection." In 1922 Davies[91] documented the presence of fecal antibody in the stools of patients with bacillary dysentery before serum antibody appeared. Subsequent observations by Heremans[92] (1960), Tomasi *et al*[93] (1965), and Bienenstock, among others, identified the IgA class of immunoglobulins and their role in the emerging field of mucosal immunity of the gastrointestinal tract. In 1938 I. Gray *et al* [94] induced an allergic reaction to a specific protein in the passive ly sensitized rectal mucosa of human subjects and the rhesus monkey and in the mucosa of the ileum and the colon in man (1940)[95,96]. The concept of an altered gut mucosal immune system in the pathogenesis of inflammatory bowel disease[97] developed in the context of a temporary interest in hypersensitivity (allergy) of mucous membranes of the gastrointestinal tract to foods, pollens, and other allergens[98,99].

Immune mechanisms in the late 1940s were implicated in various diseases of unknown etiology (e.g. rheumatoid arthritis). Several clinical events during the 1930 s and 1940s suggested to me the potential involvement of immune mechanisms in ulcerative colitis[100]. These included the abrupt onset of severe ulce rative colitis in a young woman who, with many others, had developed acute food poisoning at a family picnic in New York state; everyone recovered within 24 to 48 hours except for the patient, who developed ulcerative colitis from which she died several years later; the association of ulcerative colitis with other immune diseases (e.g. autoimmune hemolytic anemia); the ulcerative colitis developing years later in individuals who had experienced an acute amebic dysentery (1933-1934), the familial occurrences of inflammatory bowel disease, and the beneficial therapeutic effects of ACTH and the adrenal corticosteroids.

The immunologic resources and responses of the gastrointestinal tract, despite earlier observations, had not been fully appreciated. Kirsner and Palmer[101] wrote in 1954: "…Perhaps future studies should include the concept of vulnerability of the host, a person more susceptible to ulcerative colitis because of tissue hyper-reactivity." In 1956, utilizing the 1920 Auer [102] principle of local autosensitization to foreign protein, Kirsner and Elchlepp[103] produced immune complexes to crystalline egg albumin in rabbits and localized the complexes to the distal bowel via the rectal instillation of a non-inflammatory solution of very dilute formalin. An ulcerative colitis promptly developed in the same areas of the left colon demonstrated immunologically to contain the immune complexes and nowhere else. The Auer-Kirsner phenomenon was reproduced in 1963 by Callahan *et al*[104]. In colon-sensitized inbred mice. Kirsner and Goldgraber, inducing the cla ssic Arthus and the Shwartzman reactions in the rabbit colon, in 1958-1959 reconfirmed the immunologic responsiveness of the bowel.

Studies by Kirsner*et al*[105], O. Broberger *et al*[106] and by Bernier *et al*[107] had demonstrated heterogeneous hemaggluti nating and precipitating "antibodies" reacting with antigens of human colon mucosa in the sera of children and adult patients

with ulcerative colitis. Shorter[108] (1972), in recognition of the infant's more permeable in testine and immature intestinal defenses permitting the entry of bacteria and other antigens into the bowel, suggested an early "priming" of the gut mucosal immune system as "preparing" the bowel for the later development of an inflammatory bowel disease; a sequence of events similar to the earlier instances of food poisoning. Immunological interest in IBD increased and by the 1960s focused upon "autoimmunity", intestinal antigens, anti-colon anti bodies, abnormal serum immunoglobulins and an experimental immune colitis. The methodology was crude; the "antigens" and "antibodies" were inadequately characterized and a relationship to IBD was never established.

Though immune mechanisms are involved in IBD, immunologic studies, after approxi mately fifty years, have not yet demonstrated an antecedent vulnerability in patients or in healthy members of IBD families. Most of the immunologic phenomena described in IBD thus far, appearing and disappearing with the activity and quiescence of ulcerative colitis or Crohn's disease, represent secondary even ts, reflections of an over-active malfunctioning gut mucosal immune system. Nevertheless immunologic interest continues in the gut-associated mucosalimmune system, antigen-access M and dendritic cells of the intestinal epithelium, T cell antigen receptors and transgenic animal models[109]. Interest also is developing in the identification of antigen(s) (probably components of the intestinal flora) recognized by the serum anti-neutrophil cytoplasmic antibodies found in ulcerative colitis. The present view for ulcerative colitis emphasizes increased responsiveness of the gut muscosal immune system, involving Th1 T cells in Crohn's disease and Th2 T cells in ulcerativ e colitis in genetically vulnerable individuals. For Crohn's disease, immunological mechanisms also are involved in association with the intestinal inflammatory reaction probably involving a component of the intestinal flora.

M cell Two additionally important elements of the immune response in IBD are the intestinal (antigen access) M cell and the role of lymphokines / cytokines. The M (membranous) cell is a specialized epithelial cell characte rized by lumenal surface microfolds rather than microvilli overlying the gut- associated lymphoid tissues (also present in the colon and the appendix), which facilitates the selective uptake and transport of bacterial, viral, or food antigens from the intestinal lumen to the gut mucosal immune system. The membran ous (M) cell of the intestinal epithelium was identified in 1923 when Kumagai[110] demonstrated the uptake of ink, carmine dye, powdered erythro cytes, and living mycobacteria from the intestinal lumen into the rabbit appendi x and/or Peyer's patches, via specialized cells in the intestinal epithelium. In 1965 Schmedtje[111], studying the epithelium of the rabbit appendix, designated such cells overlying lymphoid follicles as "lympho-epithelial cells". Owen *et al*[112] (1974) coined the term M cells.

Inflammation, lymphokines, cytokines Cytokines are small to medium-sized proteins elaborated by "producer" cells responding to disease- inducing stimuli (injury or antigenic stimulation), influencing the behavior of particular target cells via specific surface receptors. Lymphokines is the arbitrary term applied to cytokines produced by cells involved in the immune system. Cytokines participate in the regulation of the immune response and help orchestrate the complex process of inflammation. The interrelationship of the immune response in IBD with the inflammatory process and the regulatory role of lymphocytes and cytokines are extremely important in understanding the nature of IBD.

Interest in the biology of inflammation and its involvement in immune reactions dates back nearly 100 years to the observations on cellular immunity (i. e. phago cytosis) by Elie Metchnikoff[113] in 1883, on humoral immunity by Paul Ehrlich[114] (1908), and in the 1930s and 1940s to the biochemical studies of inflammation by Valy Menkin[115]. McCord *et al*[116] in 1969 were the first to discover the enzyme superoxide dismutase (SOD) and proposed that the free radical is produced in mammalian systems. Babior[117] first demonstrated that activated polymorphonuclear cells produce large quantities of the superoxide anion radical. The possible role of reactive oxygen metabolites in intestinal injury or inflammation was first reported by Neil Granger *et al*[118] who demonstrated that post-ischemic microvascular injury in the small bowel could be attenuated by the intravenous administration of superoxide dismutase. M.B. Grisham *et al*[119] also suggested the possibility that immunologically-activated phagocytic leukocytes (e.g. PMNs, eosinophils, and macrophages) could be important contributors to the mucosal injury characterizing intestinal inflammation. In 1975, Gould[120] of England found increased levels of the cyclooxygenase derived prostaglandins (PGE_2) in the stools of patients with ulcerative colitis. Sharon *et al*[121] also noted elevated levels of prostagland ins in the colonic mucosa and the serum of patients with ulcerative colitis. The prostaglandins subsequently were identified as cytoprotective agents.

Interest in lymphokines/cytokines dates to the

1972 discovery of a factor produc ed by macrophages stimulating T cell responses to antigens, later designated as interleukin-1 (IL-1)[122] (perhaps known in the 1940s as endogenous pyrogen)[123] and to the discovery of interleukin-2 (IL-2) by Paetkau *et al*[124] and by Chem *et al*[125] in 1976. Sharon and Stenson demonstrated a 50-fold increase in the leukotriene LTB4 in the colonic mucosa of ulcerative colitis and postulated a pro-inflammatory role for LTB4 in both ulcerative colitis and Crohn's disease. Investigation of the important role of cytokines in the tissue reaction of ulcerative colitis and of Crohn's disease today is one of the most active research areas in IBD.

GENETIC ASPECTS OF INFLAMMATORY BOWEL DISEASE-EARLY OBSERVATIONS

The first published instances of familial IBD from the 1909 London symposium: (a) brother and sister, (b) father and sibling, and (c) father and siste r of a third patient, were considered "coincidences", and this view prevailed for more than 50 years. Reports of "familial" inflammatory bowel disease appeared in the 1960s and subsequently increased, indicating a genetic relations hip in IBD[126-129].

Ulcerative colitis In 1936 Moltke[130] described 5 fam ilies with ulcerative colitis. Sloan *et al*[131] (1950) noted 26 positive family histories among 2000 patients, kirsner and Palmer (1954) reported 6 family occurrences, and Banks, Korelitz, and Zetzel (1957), 9 families among 244 patients. Schlesinger and Platt (1958) obtained a family history of ulcerative colitis in 17% of 60 children with ulcerative colitis. An unusual sequence involved two brothers, who developed ulcerative colitis and succumbed to carcinoma of the colon within 15 years after onset of the disease[132]

Crohn's disease Crohn[133] in 1934 described regional ileitis in a brother and sister. Familial instances of regional enteritis subsequently were reported by other observers[134,135]. In the family described by Kuspira *et al*[136], six members were affected spanning three generations.

Familial patterns Familial distributions of IBD involved first-degree relatives (parent, child, or siblings) more often than second-degree or third-degree relatives (aunts, uncles, nieces, and nephews) in accord with a polygenic inheritance. In the 1963 Chicago study for ulcerative colitis, 50 of the 89 family members were brothers, sisters, and cousins, approximately the same generation as that of the probands and 11 were grandparents. For Crohn's disease, 15 of 22 family members involved brothers, sisters, and first- cousins. De Matteis[137] (1963) summarized 5 reports on ulcerative colitis comprising 20 parent-child combinations; mother and child were involved in 16 and father and child in 4. Among 32 reports on Crohn's disease involving 72 familial instances, mother and child were affected in 7 instances and father and child in 3.

The occurrence of IBD in three or more members of the same family, very strong support of a genetic relationship, included Spriggs (1934): ulcerative colitis in 2 brothers and a sister; Moltke (1936): brother, sister, and maternal aunt; B rown and Schieffley (1939): 2 sisters and 1 brother; Jackman *et al*[138] (1942): (a) mother, son, and mother's brother; (b) mother and 2 daughters with ulcerative colitis and nephew with regional enteritis; and Bacon (1958): tw in brothers and a sister.

Thayer's[139] (1972) family included a 21-year-old male with ulcerati ve colitis since the age of 8 who developed a carcinoma of the descending colon. A maternal aunt developed ulcerative colitis at the same time. One year after the death of the index patient, his brother, 2 years younger, developed ulcerative colitis and required colectomy and ileostomy. Within a year after this operation the boy's father developed ulcerative colitis and after 5 years of medical treatment, he also underwent a colectomy and ileostomy. The 8 members of the Morris family (1965) represented 3 generations, all with ulcerative colitis, 4 males and 4 females. The 7 affected members of the Ashkenazi Jewish f amily studied by Sherlock *et al* (1963) included 5 with Crohn's disease and 2 with ulcerative colitis. Seven IBD uninvolved relatives of the same family had varying degrees of deafness.

Intermingling of diseases-twins-genetic associations Ulcerative colitis was more likely to occur than Crohn's disease among the fami lies of probands with ulcerative colitis and a similar relationship held for probands with Crohn's disease. However, in approximately 25% of families, the dise ase incidence was mixed, suggesting a similar genetic susceptibility profile. The association of ulcerative colitis and Crohn's disease with genetically- mediated conditions, such as for ulcerative colitis: ankylosing spondylitis and Turner's syndrome; and for Crohn's disease: psoriasis and the Hermansky-Pudla k syndrome, added to the evidence. The survey of monozygotic twins demonstrated moderate concordance for ulcerative colitis and strong concordance for Crohn's disease; discordance was more common for ulcerative colitis than for Crohn's disease.

Early genetic surveys revealed an association between HLA-DR2 phenotype and ulcerative

colitis, between DR1, DWQW5 or B44C-W5 phenotypes with Crohn's disease, and HLA-DQB-1 genotype with Crohn's disease in children. Recent genetic linkage studies have identified gene loci in chromosomes 6 (possibly for ulcerative colitis), chromosome 16 (definitely for Crohn's disease), loci for chromosome 1 in the Chaldean patient population relocated near Detroit and a trend toward common genes for Crohn's disease and ulcerative colitis.

CONCLUDING COMMENT

The chronological events described for ulcer ative colitis and for Crohn's disease reveal diseases at least several centuri es old. The changing epidemiological patterns; the increases during the 19th century, especially in northern Europe and England, extending to the United States in the early 20th century; the prominence of ulcerative colitis during the first half and of Crohn's disease during the second half of this century; their frequency in the industrialized countries contrasting with under-developed cou ntries; their appearance in previously lagging, increasingly industrialized are as (e.g. Japan, Brazil), all are consistent with widespread environmental etiolo gic contributions (bacteria, viruses, and parasites, cytotoxic food additives, industrial, atmospheric, and water pollutants, chemicals, "stress", etc.) not exclusive to any particular geographic area or to any ethnic group, affecting genetically-vulnerable individuals in immune and genetically mediated complex tissue reactions.

The study of ulcerative colitis and Crohn's disease today involves many expandi ng scientific disciplines, including the biology of the intestinal epithelium, the molecular basis of inflammation, genetic, geographic epidemiology, molecular microbiology, intestinal immunology, molecular genetics and gastrointestinal neuro-endocrinology. The challenge for the next century will be to utilize these scientific advances in coordinated interdisciplinary research towards the ultima te understanding and control of two of the most intriguing diseases in medicine[140].

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