Part II

Crohn's disease

ORIGINS

Inflammatory bowel disease descriptively consistent with Crohn's disease apparently was observed three hundred years ago, possibly earlier in Carson's "Iliac Passion."[279] Wilhelm Fabry[280] (Guilhelmus Fabricius Hildanus) of Hilden-Cologne, Germany (1560–1629), had noted at autopsy in a boy who had experienced persistent "subhepatic pain" that "the cecum (was) contracted and invaginated into the ileum ... such that it was not possible for anything to pass from the proximal intestine into the colon." On extracting the cecum, it was ulcerated and fibrous. J.H. Baron,[281] in a review of early instances of possible Crohn's disease, cites J.J. Bernier et al.[282] on La Maladie de Louis XIII. Baron writes "... Louis XIII is known to have been prone to attacks of diarrhea for decades, associated with fever and a rectal abscess that discharged spontaneously. In 1642, he experienced bloody diarrhea, fever, abdominal pain and a perianal abscess or fistula. He died the following year, at age 42. Autopsy revealed ulcerations of small and large bowel, with abscesses and fistulas, compatible with ileocecal tuberculosis or regional enteritis." The noted pathologist G.B. Morgagni[283] of Forli, Italy (1682–1771) in his "De Sedibus et Causis Morborum" in 1761, described ulcerations and perforation of an inflamed, narrowed 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.

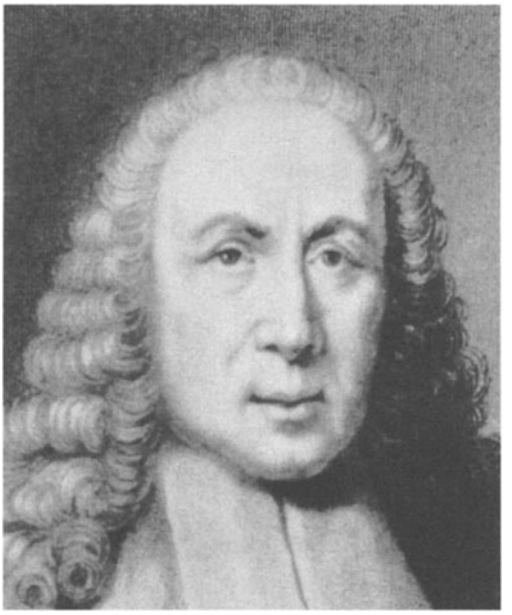
C. Combe and W. Saunders[284] (1813) of England, reporting a patient who had experienced abdominal cramps and diarrhea, wrote: "The lower part of the ileum as far as the colon was ulcerated and contracted for three feet to the size of a turkey quill." J. Abercrombie[285] (1828) of England observed an inflamed, ulcerated and thickened ileal segment in a 13-year-old girl who had suffered from diarrhea.

As reported by J. Fielding,[286,287] Abraham Colles[288] of Dublin, Ireland, as early as 1830, had described an apparent Crohn's disease among children, including perianal, rectovaginal, and rectovesical fistulas,

J. B. Kirsner, *Origins and Directions of Inflammatory Bowel Disease*

Wilhelm Fabricus Hildanus

attributed initially to tuberculosis. Corrigan[289] of Ireland in 1853 reported a patient with a thickened ileum and "snail track ulceration." Fielding,[287] noting that the disease had appeared at least since the middle of the 19th century, summarized the features in 31 patients seen in London from 1850 to 1899. The group included 11 males and 20 females, with ages from 5 to 59 years. The disease involved the large bowel in 15, the small and large bowel in 12 and the small intestine only in 4. Findings included enlarged mesenteric lymph nodes, toxic dilatation of the bowel, free perforation of the intestine and liver disease (fatty infiltration, hepatitis). Fielding also tabulated the findings in 25 additional patients considered as "possible Crohn's disease." A review of the Transactions of the Pathological Society of London for the same period included: N. Moore's[290] (1882) first microscopic description of Crohn's disease and case reports by S.J. Sharkey (1884), R.E. Carrington (1886), and C. Ogle (1895). "It is of interest that the large majority of cases involved the large bowel." J.F. Walker and J. Fielding[291] compiled 29 additional 19th century instances of apparent Crohn's disease from Dublin hospitals during the same period. The Dublin series included 19 males and 10 females, ages 16 to 68. The large bowel was affected in 8, large and small bowel 15 and small intestine in 6.



G.B. Morgagni

Interesting features included extracutaneous fistulas, entero-vesical fistula, intra-abdominal abscesses, one instance of toxic dilatation of the colon, free bowel perforations, and perianal suppurative disease. In a 25-year-old male patient, "the contraction (in the colon) was so great that a common crow quill could scarcely be passed through it."

J.S. Bristowe[292] (1853) of London found at autopsy in a 32-year-old woman with a history of persistent diarrhea narrowing and ulceration of the mid jejunum and ileum; the ileum was thickened, the lumen narrowed, a fistula involved several segments of the ileum and the colon was ulcerated and perforated. As noted earlier, the transmural "ulcerative colitis" described by Samuel Wilks[19] in 1859 (patient Isabella Bankes) was re-classified in 1970 by J. Fielding[293] as Crohn's disease of the colon. In 1889 Samuel Fenwick[294] of London, in a 27-year-old woman with a history of diarrhea and weight loss, wrote: "Many of the coils of intestine were adherent and a communication existed between the cecum and a portion of the small intestine adherent to it. Whilst the sigmoid flexure was adherent to the rectum and a communication also existed between them, the lower end of the ileum was much dilated and hypertrophied and the ileocecal valve was contracted to the size of a swan's quill."

H.I. Goldstein[295] of Camden, New Jersey (USA), in a paper entitled the History of Regional Enteritis, begins: "In the American Medical and Philosophical Register or Annals of Medicine, Natural History, Agriculture and the Arts conducted by a Society of Gentlemen, New York (Volume I, July 1870), John Wakefield Francis of New York reports a case of enteritis accompanied with a 'preternatural formation of the ileum,' suggestive of Crohn's disease." G. Hellers[296] of Stockholm in his monograph (Crohn's disease in Stockholm County 1955–1974) states: "Between 1870 and 1900, case histories of all inpatients in the Surgical Department at the Serafimer Hospital (Stockholm) included a case described by John Berg (1898) possibly due to Crohn's disease. The patient, a 20-year-old man, was admitted after a three weeks' illness, in very poor condition and with a mass in the right iliac fossa. At operation, a thickened ileum was found with several mesenteric abscesses. A normal appendix was removed. The patient died on the second day. Postmortem examination revealed perforation of the bowel and peritonitis." Heller adds that a 1932 thesis by Strombeck[297] entitled Mesenteric Lymphadenitis included 349 patients. "Most of these cases were probably due to acute terminal ileitis but some may well have been due to Crohn's disease." While conclusive diagnoses were not possible several centuries earlier, these early reports similar in clinical and anatomic features represented the emergence of an inflammatory intestinal disorder later designated as Crohn's disease.

EARLY CLINICAL RECOGNITION

The early years of the 20th century were characterized by increasing recognition of patients with "regional enteritis," descriptions of associated clinical problems and by limited attempts to clarify the nature of this entity. The first important observation was by A.J. Lartigau,[298] pathologist at Columbia University (New York). In a 1901 detailed study of "a form of tuberculosis of the small intestine," characterized by pronounced thickening of the wall of the intestine, he reviewed the already substantial German and French literature on the subject, noted the first such case recognized by Hartman and Pilliet[299] in 1891 and astutely described in detail the unique case of Simon S., age 49, who in 1895 succumbed after three years of symptoms, including weight loss, abdominal cramping pain, alternating diarrhea and constipation and darkening of skin color. Autopsy demonstrated no evidence of pulmonary tuberculosis. The liver and gallbladder were normal. The major finding was thickening of the distal two thirds of the intestine, involving the cecum and a thickened and

rigid ileocecal valve. Although the initial "diagnosis" was hyperplastic tuberculosis of the small and large intestine, Lartigau noted several critical differences: many "tubercles" were mere aggregations of lymphoid cells with occasional giant cells, without epithelioid cells and, in contrast to tuberculosis, "with little or no tendency to necrotic change." The typical histologic features of tuberculosis were absent. These histologic findings in modern times are consistent with Crohn's disease and Lartigau probably was the first to recognize the histologic difference from tuberculosis and define an important feature of Crohn's disease. The long-time significant involvement with pulmonary and intestinal tuberculosis clearly had influenced physicians, unaware of the "new" entity of "Crohn's disease," to overlook this diagnosis.

The early case reports by Braun[300] (1901), J. Koch[301] (1903), Wilmanns[302] (1905), H. Senn (1905) and H. Lilienthal (1906) of the United States, Moynihan[303] (1907), R. Proust[304] (1907) and Lejars[305] (1908) of France, Monsarrat[306] (1907) of Liverpool, England and von Bergmann[307] (1911) of Germany, (cited by Shapiro[308]) were noteworthy for their presentation as abdominal (inflammatory) masses, clinically resembling tumors, assumed erroneously to be "malignant" and, at a time of limited abdominal surgery, were assessed by clinicians, unaware of IBD, as "untreatable." R. Shapiro's[308] 1939 review (289 references) identified many instances of apparent Crohn's disease masquerading as "tumors." Two hundred and sixty one of the 413 cases collected from the literature in this report involved the terminal ileum and 22 the right colon. E.G. Janeway[309] of New York had presented a similar paper ("Inflammatory Abdominal Masses Simulating Malignant Growths") at the 1907 annual meeting of the Association of American Physicians in New York and N.M. Jones and A.A. Eisenberg[310] (1918) of Cleveland, Ohio reported a similar patient; neither paper attracted attention. E. Schmidt[311] (1911), (Dresden, Germany), S. Goto[312] (1912) (Fukuoka, Japan) each described patients misdiagnosed initially as "intestinal cancer," with pathologic features resembling Crohn's disease. Since these publications antedated the recognition of Crohn's disease, the central issue at the time was the masquerading of intestinal inflammatory "masses" as abdominal tumors.

The landmark 1913 paper by T. Kennedy Dalziel,[313] a Glasgow surgeon, antedating Crohn's paper by nearly 20 years, included 13 patients and was the second important clinical development, a model of accurate clinical description. The first case, a physician, since 1901 had experienced episodes of cramping abdominal pain and diarrhea progressing to intestinal obstruction. At autopsy, the entire small intestine was

Sir T. Kennedy Dalziel

chronically inflamed and narrowed and the mesenteric lymph nodes were enlarged. In another patient, "The affected bowel gives the consistence and smoothness of an eel in rigor mortis, and the mesenteric glands, though enlarged, are evidently not caseous." In other patients, the process involved the jejunum, midportion of the ileum, and the transverse and sigmoid colon. Histologic examination demonstrated vascular congestion, submucosal edema, acute and chronic transmural inflammation, increased numbers of eosinophils and scattered giant cells. Dalziel distinguished the process from tuberculosis and related his "chronic intestinal ileitis" to Johne's disease of cattle (M. paratuberculosis) described first in 1895 and publicized by McFadyean in 1907.[314] Crohn's disease recently has been differentiated from Johne's disease by Van Kruiningen.[315] Although Dalziel had presented his paper at the 81st annual meeting of the British Medical Association, it was unnoticed for many years.

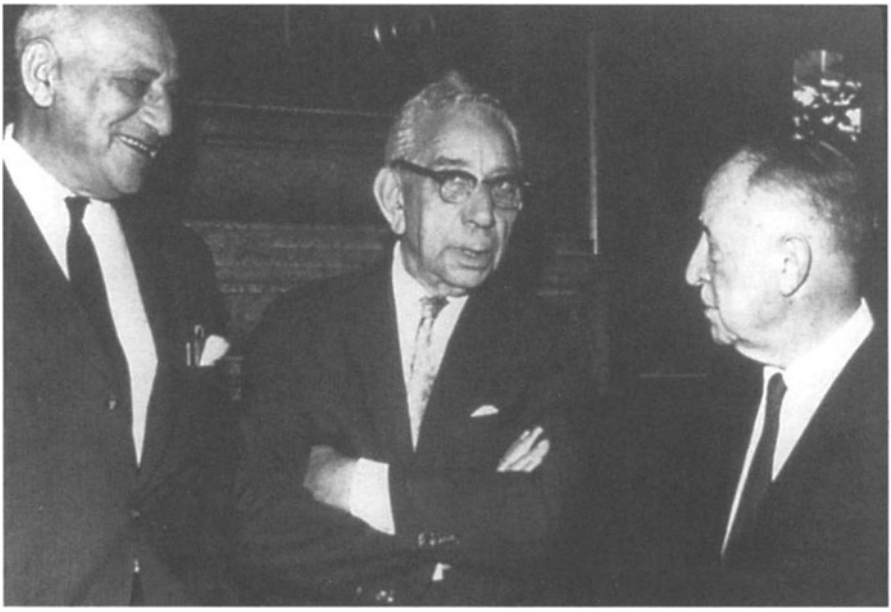
In 1914 A. Läwen[316] of Leipzig, Germany in a 20 page report described an "appendicitis fibroplastica," simulating a tumor. Twenty four years later from Königsberg, Läwen, now aware of the paper by Crohn, Ginzburg, and Oppenheimer, reported the identical patient, re-evaluated as a "chronic stenosing terminal ileitis,"[317] illustrating the impact of new information in

physician recognition of previously overlooked clinical and pathologic entities (Goethe: "was man weiss, man sieht"). By 1920 Tietze[318] of Breslau, Germany had reviewed 281 cases from the medical literature. Korte[319] of Berlin (1921) and Bundschuh and Wolff[320] (1925) Wurzburg, Germany each described groups of patients with similar findings, reviewed the considerable early German literature (Korte – between 1908–1920) (Bundschuh and Wolff – between 1895–1924) respectively and concluded in 1925 that "chronic ileitis" was more common than had been appreciated.

By 1925, American physicians began to increasingly report instances of "nonspecific" hyperplastic and granulomatous lesions of the intestinal tract, previously labelled "intestinal tuberculosis." T.H. Coffen[321] of Portland, Oregon in 1925 described a clinical situation familiar today. A 20-year-old man with abdominal cramping pain since 1915 underwent surgery in 1916 because of small bowel obstruction, with resection of six inches of thickened inflamed bowel. Five months later, 24 inches of bowel were removed for recurrent obstruction. Eight months later, 24 inches of bowel were removed for recurrent obstruction. Eight months later, a fourth bowel resection was necessary for obstruction, emphasizing not only the cicatrizing nature of Crohn's disease but also the individually consistent recurrence of the same complication.

The 1932 paper by Crohn, Ginzburg and Oppenheimer,[322] the third significant event, dramatically increased clinical recognition of regional ileitis (Crohn's disease); approximately 500 cases were reported in the medical literature during the four year period 1932 to 1937! H.W.L. Molesworth[323] of England in 1933, in a 33-year-old woman with the history of an appendectomy in 1921, found at surgery for intestinal obstruction, hypertrophy of the small intestine, thickening of the terminal ileum and adjacent mesentery and stenosis of the ileocecal valve. The mimicry of intestinal neoplasm by "chronic cicatrizing enteritis" (Crohn's disease) was re-emphasized by Donchess and Warren[324] of Boston in a 1934 case report: a 62-year-old woman, with involvement of the cecum and the ascending colon. Twenty-four similar instances, often with appendiceal involvement, recorded in the literature during the 1920s and 1930s were reviewed.

Many reports expanded the clinical spectrum of regional enteritis.[325–331] Brown, Bargen and Weber[332] in 1934 and Pemberton and Brown[333] in 1937 reviewed their considerable experience with regional enteritis at the Mayo Clinic dating back to the 1920s. The clinical and pathologic features in all patients were similar, regardless of geography, age (children, teen-



G. Oppenheimer, B. Crohn and L. Ginzburg

agers, and young adults), symptoms of abdominal cramps, diarrhea, low grade fever, and weight loss, often presenting as acute "appendicitis" and treated by appendectomy. In 1933, Harris et al.[334] recorded involvement of the jejunum and the colon. Also in 1933, American surgeons Homans and Hass[335] described regional ileitis as "a clinical not a pathological entity." Anal disease and fistula formation had been noted in the 1932 paper by Crohn et al. and these findings were emphasized in 1934 by A.D. Bisell,[336] R.J. Jackman[337] (1943) and later (1965) by Gray, Lockhart-Mummery and Morson.[338] In 1934 G. Anschutz[339] of Kiel, Germany, apparently unaware of the 1913 Dalziel and 1932 Crohn papers on regional enteritis, described in detail a series of patients with chronic inflammation of the small intestine clinically resembling malignant abdominal tumors. Gastroenterologist J.L. Kantor[340] of New York in 1934 reported observations identifiable today as late roentgen findings in six private patients with regional enteritis (rigid, narrowed terminal ileum). Dyer et al.[341] (St. Bartholomew hospital, London), also emphasized contraction and rigidity as two signs with low observer variation. The expert IBD radiologist R. Marshak[342] of Mt. Sinai Hospital, New York, based upon his extensive experience with regional enteritis as the radiologist for B. Crohn et al.,

described the roentgen findings in meticulous detail and Crohn's 1949 monograph on regional ileitis included this authoritative information.[343]

ANIMAL AND EXPERIMENTAL CROHN'S DISEASE

In 1934 H.G. Bell[344] of California reported (without details) that experiments "interfering with the blood supply of the intestinal tract" had failed to produce a cicatrizing enteritis, ulceration of the mucosa or any lesion resembling regional enteritis. The early concept of a possible endolymphangitis (subcutaneous lymphatic dilatation and lymphoid prominence) as observed in resected bowel from three patients with cicatrizing regional enteritis (thickening of bowel wall, engorged lymphatics) resembling chronic lymphedema of the extremities, was the rationale for the 1936 experiments of Reichert and Mathes of Stanford University.[345] Adopting the method of Homans, Drinker and Field[346] of the Massachusetts General Hospital, Boston, Massachusetts, at intervals of weeks to months, they repeatedly injected fine sand (crystalline silica (200 mesh) or sodium morrhuate) and a sclerosing solution of 26% bismuth oxychloride, rose aniline dye (indelible lead) with and without E. coli into the cannulated mesenteric lymphatics of dogs. Chronic edema of the ileocecal area developed; mucosal inflammation, ulceration or granulomas were not observed. In 1941 J.K. Poppe[347] of Yale University, New Haven, Connecticut, seeking to reproduce an "ulcerative colitis," similarly injected a 26% aqueous solution of bismuth oxychloride with and without bacteria (B. coli, Streptococcus viridans, Staphylococcus aureus and Streptococcus hemolyticus) into the intestinal lymphatics, made prominent by a prior fat meal in 15 dogs. Lymph nodes draining the injected segments of intestine were inflamed and ulcerations of the small and large bowel developed but neither ulcerative colitis nor Crohn's disease was duplicated. Sinaiko and Necheles[348] of Michael Reese Hospital, Chicago, in 1946 injected seven dogs with bismuth oxychloride solution and sodium morrhuate (without bacteria) producing only partial obstruction of intestinal lymphatics; they attributed Poppe's findings to vascular thromboses rather than to lymphatic obstruction. Emphasizing inflammation of intestinal lymphatics or an etiologic possibility, Chess et al.[349] of the University of Illinois (Chicago) in 1950 instilled suspensions of 200 and 400 mesh sand or talc powder into Thiry-Vella fistulas of an isolated loop of terminal ileum and also fed dogs finely ground silica and talc. A mixture of S. aureus, Streptococcus and E. coli organisms was injected intravenously in one dog. Gross findings included bowel thickening, friable mucosa and hemorrhagic areas.

Histologic changes included lymphoid hyperplasia, enlarged mesenteric lymph nodes and granulomatous lesions on the liver. Talc was thought to be more pathogenic than finely divided sand. The authors compared the pathologic changes to those of regional enteritis. Kalima et al.[350] (1976) of Finland injected dilute formalin solution into the mesenteric lymphatics of the terminal ileum in 21 pigs ("chosen because spontaneous ileitis is common in pigs"). Endolymphangitis developed with congestion and edematous thickening of the distal small bowel and ileocecal area and mucosal ulceration. Histologic examination demonstrated inflammation of the subserosa with occasional foreign body giant cells, not Crohn's disease. Transmural inflammation developed after three weeks. Kalima et al.[350] stated: "The early phase of Crohn's disease includes mucosal aphthoid ulcerations, hyperplasia of intestinal lymphoid tissue with superficial ulcerations, crypt abscesses and obstructive lymphedema. The advanced phase of Crohn's disease is characterized by: (a) a transmural inflammatory process, (b) mucosal ulcerations and entero-enteric or enterocutaneous fistulas, (c) fibrosis and (d) inflammation in the serosa and mesentery." Kalima's conclusion: "Changes caused by lymphatic obstruction do not enlighten the etiology of Crohn's disease." Kalima, Saloniemi and Rahko[351] also described a "lymphostatic enteropathy," characterized by partial or total lymphatic obstruction of intestinal lymph vessels ... "closely related to many clinical diseases." Warren and Sommers in 1948 considered the possibility of an endolymphangitis in Crohn's disease, attributable to the intestinal absorption of an (unidentified) lipid but this possibility was not pursued.

Van Patter and Bargen et al.[352] in a 1954 review of 600 patients with Crohn's disease, suggested, as had earlier observers, that "the causative agent may be found in the fecal stream and ... appears initially in the proximal part of the small intestine. If this agent resides in the fecal stream, it may exert its influence on the normal epithelial cell. The further course of the agent appears to be by way of the lymphatic vessels where it causes focal intralymphatic endothelial hyperplasia, lymphatic obstruction, and dilatation, lymphoid hyperplasia and lymphatic endothelial proliferation." Bargen,[353] in a 1955 reprise of the Van Patter article, rejected bacterial, viral, and protozoan agents, sarcoid and abdominal trauma as causes, but accepted "intestinal allergy" as a possibility.

Early Crohn's disease, in its gross and histologic features, to some observers resembled the porcine terminal ileitis described from Copenhagen in 1951.[354,355] Emsbo of the Royal Veterinary and Agricultural College, Copenhagen, in a comprehensive article on porcine terminal

ileitis,[354] wrote: "In a couple of cases I too have encountered familial occurrences of ileitis in several pigs of the same litter." As evidence of the predisposition of the porcine ileum to pathological changes, he noted: the frequent occurrence of uncomplicated hypertrophy of the bowel, the often pronounced hyperplasia of Peyer's patches, the presence of epithelial changes, local fibrosis and foreign-body giant cells in the lymph follicles. However, the histologic findings were not comparable to those of Crohn's disease, including an absence of granulomatous changes. No specific organism was identified in the Danish porcine ileitis. Emsbo was convinced that porcine ileitis and human ileitis "fundamentally are identical." A campylobacter-type organism was isolated in Scottish and Swedish pigs[356] and a corona virus-like particle was associated with diarrhea in Belgian swine.[357] Strande, Sommers and Petrak[358] (Angell Memorial Animal Hospital, Boston – 500 autopsies annually) described morphologic features consistent with regional enteritis in two cocker spaniel dogs and raised the question of an infection transmitted by animals. As described by N.K. Mottet,[17] in one instance, lesions involved the colon and rectum and the terminal 6 cm of ileum with skip areas. The microscopic features included chronic inflammation with cicatrization of the intestinal wall producing an obliterative lymphangitis. Similar changes were present in the mesenteric and regional lymph nodes. Geil, Davis and Thompson,[359] Fitzsimmons General Hospital, Denver, Colorado, described a spontaneous ileitis in albino rats histologically different from human regional ileitis and the regional ileitis of swine. Cross et al.[360] of the Ohio Agricultural Research Center in 1973 described a terminal ileitis involving the distal 50 to 75 cm in 7 lambs ranging in age from 4 to 6 months. Intestinal nematodes were not found, bacterial cultures were negative. The predilection for the terminal ileum in animals, as in humans, is intriguing and deserves further study (?increased microbial adhesion sites).

Investigating staphylococcus related pseudomembranous enterocolitis, J. Prohaska[361] (University of Chicago) produced an enterocolitis in (a) chinchillas given multiple antibiotics, preparatory to the oral administration of S. aureus and (b) in mongrel dogs given single infusions of Staphylococci purified enterotoxin. Van Kruiningen[362] and Kennedy and Cello[363] reported histologic abnormalities resembling regional enteritis in Boxer dogs and favored a microbial-viral etiology for Crohn's disease. Limited microbiological studies and attempts to transmit the disease experimentally were unsuccessful. Cimprich[364] of the University of Pennsylvania Veterinary Medical School, in 1974 described a "granulomatous enteritis" in 10 malnourished horses. Bacterial, fungal and acid

fast stains were negative in nine animals, acid-fast organisms (avian tuberculosis) were identified in one horse. In 1991 Roediger[365] of Woodsville, Australia, noting that "the stimulus for the immune response in Crohn's disease is unknown," proposed an unusual "updated lipid theory." In each of 19 cases of Crohn's disease evaluated by electron microscopy, he had observed that epithelial cells of the ileum contained phagolysosomes with lamellar layers of lipid. These structures, termed R or reactant bodies, he suggested were the proffered antigenic stimulus, as an amalgam of lipid (cholesterol esters, or phospholipids) and bacterial fragments (mycoplasma, mycobacteria or streptococci), presumed to induce a powerful immunological adjuvant response. For disease expression to occur, lipids and specific bacterial populations were required in the bowel lumen.

As noted by Pizarro et al.,[366] "the more recent availability of genetically engineered mouse models of CD provided an exceptional opportunity to identify the complex mechanisms involved in the pathogenesis of human IBD" (e.g. interleukin-10 deficient mice). Elson, Sartor, Tennyson and Riddell[367] commented in 1995: "no animal model exactly reproduced these human diseases ... However, multiple models are available to study the major components involved in IBD and today these serve as an important complement to the studies of IBD in humans."[368–370] The animal studies already have suggested multiple pathogenic pathways to IBD.[371] Indeed, Kosiewicz et al.[372] recently described a new murine model of spontaneous gastrointestinal inflammation that, according to W. Strober et al.,[373] "bears remarkable similarity to human Crohn's disease," the Sampl/yit mouse. The development of the disease is dependent upon a "benign intestinal microflora."

ABDOMINAL TRAUMA

In 1932 G. Pupini[374] of Italy described a post abdominal traumatic narrowing of the small bowel resembling Crohn's disease. A.W. Fischer and H. Lürmann[375] of Germany in 1933 and Blumenthal and Berman[376] of the USA in 1939 reported similar cases. After operating on a 22-year-old motorcyclist who developed a severe jejunitis of the proximal jejunum following a severe blow to the abdomen[377] when he ran into the rear end of a truck, abdominal trauma was investigated by M. Spellberg and A. Ochsner[378] of New Orleans as a possible cause of regional ileitis. Experimental constriction of the small bowel of dogs by steel clamps produced gross lesions of the intestine but not regional ileitis. Two

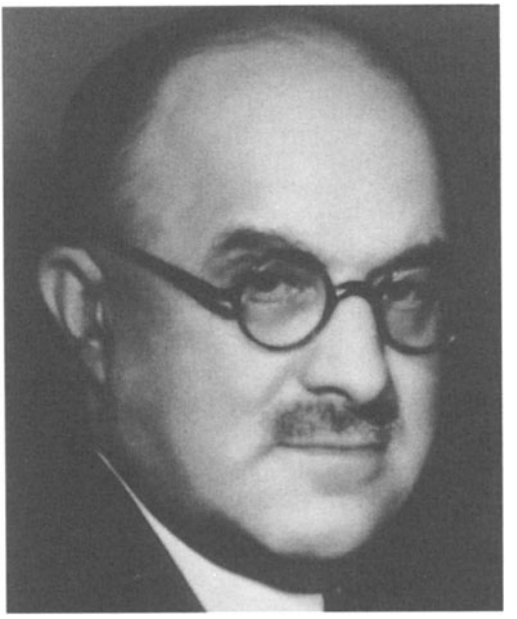
instances of "regional enteritis" following external trauma were reported from the Mayo Clinic.[379] Crohn and Yarnis[380] added 11 patients with a history of abdominal trauma but, as noted by Kyle et al.,[381] this possibility was invalidated by the vast majority of CD patients without any history of abdominal trauma.

THE EARLY MT. SINAI (NEW YORK) EXPERIENCE

Antedating the 1932 "CGO" paper, A.H. Aufses Jr.[382] cited patients admitted to the Mt. Sinai (NY) Hospital in 1855, 1889, 1899 and 1919, with clinical findings suggestive of Crohn's disease (fistula in ano, abdominal abscess with enterovesical fistula, "hyperplastic colitis," right lower quadrant mass in 23-year-old male). Aufses also described the pivotal surgical approaches to the disease throughout the years by Mt. Sinai (NY) surgeons. Immediately preceding the paper by Crohn, Ginzburg, and Oppenheimer[322] in 1932, F.J. Nuboer[383] of Holland had described two male patients with "chronic phlegmonous ileitis" and implicated an "abnormal intestinal microflora" secondary to an "achylia gastrica." M. Golob[384] of New York (1932) had reported a "chronic infectious granuloma" of the ileocecal region in a 44-year-old man who had bled per rectum.

The New York Mt. Sinai experience actually began with E. Moschowitz and A.O. Wilensky, who in 1923[385] and 1927[386] described patients with "nonspecific" granulomas of the intestine, reflecting the long-time interest of that institution in intestinal granulomas and its early commitment to medical-surgical gastroenterology. The 1923 paper described four young patients, each with a history of appendicitis and an appendectomy. The colon was involved in three and the small intestine and colon in the fourth. The 1927 paper described an 18-year-old male with an apparent acute appendicitis, perforation and abscess formation. One week after operation a fecal fistula developed necessitating a second operation. Mock[387] of Northwestern University, Chicago, aware of the 1923 Moschowitz/Wilensky paper, in 1931 described 10 patients with "infective granulomas" involving various parts of the gastrointestinal tract, including the small intestine and the colon. The lesions were evaluated in the context of chronic inflammatory masses simulating tumor and not in relation to Crohn's disease.

The decisive 1932 Mt. Sinai events appeared to be as follows: Leon Ginzburg,[388] associated with the noted surgeon A.A. Berg, who had operated on all the Mt. Sinai patients, first as Berg's resident and then his



Eli Moschcowitz

A.O. Wilensky

colleague, and Gordon Oppenheimer, then resident in surgical pathology, in studies beginning in 1925, had collected a group of 12 patients dating back to 1920, characterized by an hypertrophic and ulcerative stenosis of the distal two or three feet of the terminal ileum, "ending rather abruptly at the ileocecal valve." Ginzburg's early involvement in the study of the intestinal granulomas was acknowledged by Crohn in 1945.[389] Amebiasis, syphilis and actinomycosis, Hodgkin's disease or lymphosarcoma were eliminated as possible causes by histologic examination. Intestinal tuberculosis, the chief differential diagnostic problem of the time, was excluded by negative chest X-rays and negative Von Pirquet and intradermal tuberculin tests and by the absence of acid-fast bacilli histologically. In cooperation with pathologist William Antopol, the granulomas were evaluated as incidental findings. Fistula formation was a constant feature. However, as discovered by J.H. Baron[281] of England in his account of the Mt. Sinai (NY) terminal ileitis story and the L. Ginzburg–B. Crohn relationship (and brought to my attention by Dr. Henry Janowitz – November 2000), it is historically important to note that L. Ginzburg[390] presented a paper entitled "Nonspecific Granulomata of the Intestines (Inflammatory Tumors and Strictures of the Bowel)" "in conjunction with Burrill B. Crohn," at the May 2–3, 1932 meeting of the American Gastroenterological Association (Transactions Thirty-Fifth Annual Meeting of American Gastroenterological Association, Hotel Traymore, Atlantic City, N.J.), a publication with limited circulation. The paper was published later in the 1933 Annals of Surgery[391] and is noteworthy for its accurate description of terminal ileitis, chronologically antedating by one month the June 1932 paper by Crohn et al. The fifty-two cases comprising the Ginzburg study previously had been diagnosed as "malignancy" or "localized hypertrophic tuberculosis." An abdominal mass was palpable in every subacute and chronic case. Approximately half of the group had previous appendectomies. Chronic, incomplete small intestinal obstruction was the most common clinical manifestation.

Clinically, the patients were divided into 6 groups, some overlapping: (1) Pericolonic or peri-intestinal granulomata due to sealed-off perforation, (2) intestinal stenosis due to known vascular lesions of the bowel, (3) localized hypertrophic ulcerative ileitis, (4) localized hypertrophic colitis, (5) penetrating ulcers of the colon, and (6) granulomata secondary to inflammation of appendages or diverticula of the bowel.

All patients were operated upon by Dr. A.A. Berg. In Group 3, the terminal ileum was the exclusive site of the process. The end stage, the one most frequently observed, was conversion of the terminal ileum into a

thickened hose-like tube. The mucosal folds were partially destroyed with polypoid excrescences. Linear or oval ulceration along the mesenteric border was a constant finding. The submucosa was "enormously thickened and the bowel lumen was greatly narrowed." Microscopic examination disclosed acute and chronic inflammation; numerous non-caseating giant cells, pronounced fibrous proliferation, many lymphocytes, monocytes, plasma cells, occasional polymorphonuclear cells and areas of lymphoid hyperplasia.

In the ensuing discussion, H. Bockus raised the question of "undue ptosis rotating the ascending branch of the ileocolic artery supplying the terminal ileum, causing vascular insufficiency." W. Alvarez stated he had seen instances of terminal ileitis but had not appreciated their significance. He suggested as a possible mechanism, "reversal of the intestinal gradient in the terminal ileum." B.B. Crohn, showing four slides, indicated he had been interested in the problem "for some time." He noted the fourteen cases with which he was familiar (two, his patients, 12 from Ginzburg and Oppenheimer), the tendency to intestinal stenosis and obstruction and to fistula formation. He added that three, four or five cases were seen each year at Mt. Sinai Hospital and that the condition was more common than had been appreciated. Ginzburg dismissed the etiologic possibilities of amebic infection, syphilis or vascular insufficiency and concluded that the etiology was yet to be determined.[392]

As an intern at New York's Mt. Sinai Hospital (1907–8) Burrill Crohn (1884–1983) had participated "in all autopsies, to cut and to take dictation on all surgical sections." In 1930 Burrill Crohn (now Dr. Berg's gastroenterology consultant) had under his care two young patients with a similar process. Crohn's first case seen in 1930 was a 17-year-old young man with diarrhea, fever, a mass in the right lower abdominal quadrant, and pain, requiring ileocecal resection. The patient's sister also was operated upon for regional ileitis several years later.[393] As related to me by Henry Janowitz of Mt. Sinai Hospital, the two groups united at the recommendation of surgeon Dr. A.A. Berg and chief pathologist Dr. Paul Klemperer, providing the 14 cases published in the 1932 JAMA article as "terminal ileitis." The article was credited to the surgical service of Dr. A.A. Berg and had Berg accepted the invitation to join the alphabetically arranged authorship of the paper, we might today be writing about Berg's disease! At the time the paper was presented in New Orleans (May 13, 1932), J.A. Bargen of Rochester, Minnesota, wisely anticipating the more extensive involvement of the small intestine, suggested the term regional enteritis. As noted earlier, Ginzburg, with G. Oppenheimer, "had been

studying the pathology and clinical features of patients with intestinal granulomas of various origins and instances of distal ileal stenosis for many years; and his claim for eponym co-designation (Crohn–Ginzburg–Oppenheimer or "CGO" disease) seems justified.

R. Lewisohn,[394] on the Surgical Service of Mt. Sinai, New York in 1938, aware of regional enteritis in other areas of the small bowel and also in the colon, preferred the term "segmental enteritis." Lewisohn wrote further: "... As our views on ileitis and ileocolitis stabilize with accumulated experience during the next few years, this lesion may turn out simply to represent a milder form of ulcerative colitis." Although reports of regional ileitis were increasing, clinical and investigative interest in the new entity remained low. Crohn,[395] reviewing his Mt. Sinai experience later, queried: "Are these new diseases the product of our modern civilization in the nature of psychosomatic disease or the end product of the industrial revolution?" The significant contributions of Mt. Sinai Hospital (New York) physicians to the knowledge of regional ileitis have been collected by D. Sachar.[396] Kovalcik of Eastern Virginia Medical School[397] in 1982 provided an "outside" perspective on the Mt. Sinai story.

MORE EARLY 20TH CENTURY REPORTS (CD)

Emphasizing the frequent need for surgery, in 1933 A.W. Fischer and H. Lürmann[375] of Frankfurt am Main, Germany described 3 patients with regional enteritis; each had presented with tumor-simulating inflammatory abdominal masses, in one instance associated with perforation of bowel. In the same year, J.F. Erdmann and C.V. Burt[398] of the New York Postgraduate Medical School, apparently unaware of the 1932 paper on regional ileitis, added 5 similar cases. In 1934 Brown, Bargen and Weber[332] describing involvement of the entire ileum and jejunum, validated the term "regional enteritis." In 1934 A.S. Bisell[336] (University of Chicago) described two male patients, ages 28 and 39, with ileocecal masses and a fistula requiring resection. Corr and Boeck[399] (Los Angeles, California) almost simultaneously contributed additional instances of the disease. Harold Edwards[400] of London in 1936 characterized the resected bowel from a 23-year-old woman, who had been treated for abdominal tuberculosis, as having the "consistency of a hose pipe." He added: "Recurrences sometimes occurred at the anastomotic site ... it was well to remember that Crohn's disease was a rather fatal condition, about half the cases dying." In his 1968 Bradshaw lecture on Crohn's disease before the Royal College of Surgeons of England, Edwards[401] agreed with Meadows

A.A. Berg

and Batsakis[402] (1963) of Ann Arbor, Michigan "that the main early feature ... of Crohn's disease is a pronounced edema of the entire bowel wall, most marked in the submucosa and accompanied by a hyperemia and lymphangiectasis." Appendicitis was the initial diagnosis in one-third of 240 patients. The 1936 series of Koster, Kasman, and Sheinfeld[403] of Brooklyn, New York included "17 instances of peculiar inflammatory lesions localized in the terminal portion of the ileum." The preoperative diagnosis had been appendicitis in 13 of the 17 patients. In 1936 Crohn and Rosenak[404] reported 9 instances of combined ileitis and colitis, another early indication of Crohn's disease of the colon. Also in 1936 A.A. Berg[405] (Mt. Sinai Hospital, New York) had described an operative procedure for "right-sided ulcerative ileocolitis" ("ulcerative colo-ileitis") "to put the diseased colon at rest," provide "an outlet" for the discharge of blood and pus and "cleansing of the diseased colon by irrigating fluids."

R.A. Leonardo[406] of Rochester, New York in 1937 described the interesting course of a 33-year-old white male hospitalized in 1935 for abdominal cramps and diarrhea, diagnosed as "early appendicitis." One year earlier, a lesion on his face had been resected, described histologically as "lymphoid tissue with many characteristic tubercles" and diagnosed as

tuberculous lymphadenitis. An appendectomy (retrocecal appendix) was performed with "more than the usual amount of trauma to the ileocecal region." Within days the patient was re-hospitalized with abdominal cramps and diarrhea. Laboratory studies were unremarkable. X-rays indicated small bowel dilatation. At operation, a large inflammatory mass involved the last 8 inches of terminal ileum, the cecum and 4 inches of the ascending colon. The mesentery of the terminal ileum was greatly thickened and the terminal ileum was adherent to the peritoneum. No tubercles were identified histologically. The differential diagnosis included: operative trauma (preceding operation), tuberculosis of the cecum (negative chest X-ray) or carcinoma. A simple ileostomy was performed. Within days, all symptoms disappeared and the patient apparently had no further difficulty. The author, aware of the 1932 paper on regional ileitis, diagnosed combined "regional ileitis" and colitis. The favorable course after the "simple ileostomy" was an early indication of the benefits of diversion of the fecal stream. In retrospect, the facial lesion probably was "metastatic Crohn's disease!"

I. Snapper and A. Pompen[407] of Amsterdam, Holland (1936), describing five patients, implicated "intestinal stagnation" proximal to the ileocecal valve, recognized the clinical similarity to acute appendicitis, and the tendency to fistula formation and suggested its higher frequency among Jewish individuals. T.G.I. James[408] of England in 1937, describing an inflammatory mass with histologic features of Crohn's disease involving the transverse colon in a 19-year-old male, was an early advocate of the entity of Crohn's disease of the colon. In 1937 Jellen[409] of Los Angeles, California (formerly radiologist at Mt. Sinai) reviewed the clinical features in fifty patients with regional ileitis ("nonspecific ulcerative granuloma") with emphasis upon the roentgen findings. I.S. Ravdin and C.G. Johnston[410] University of Pennsylvania, in 1939 suggested twelve possible etiologic factors: (1) bacteria, (2) bacterial toxins, (3) viruses, (4) protozoa, (5) metazoa, (6) achylia gastrica, (7) allergy, (8) foreign bodies, (9) nonspecific inflammation of appendix, (10), impairment of blood supply, (11) interference with lymphatic supply and (12) trauma.

By the latter 1930s, Crohn's disease was global in distribution, with reports from Italy,[411,412] Sweden,[413] Germany,[414] Holland,[415] Australia[125] and later among Chinese in Hong Kong[416] and among Chinese immigrants to Vancouver, British Columbia, Canada.[417] In 1937 C. Gottlieb and S. Alpert[418] (Lincoln Hospital, New York) described the roentgen appearance of regional jejunitis in a 44-year-old Greek man; the diagnosis, suspected on X-ray, was confirmed at abdominal operation. In

1940 Sherrill and Hall[419] of Nashville, Kentucky, reported two interesting cases of regional ileitis. In one, a 17-year-old male presented with intestinal obstruction caused by a thickened adherent distal ileum necessitating operation. In the second instance, a 16-year-old male presented with abdominal pain and fever, found at operation to be caused by a Meckel's diverticulitis enveloped in the ileitis. The ileum was thickened and adherent with pronounced fibrosis of the distal ileum necessitating bowel resection. In 1943 A. Tallroth[420] of Gothenberg, Sweden impressed by the large numbers of eosinophils in the inflammatory reaction, considered "intestinal allergy" as the underlying mechanism.

A detailed clinical report by E. Schiff[421] of Basel, Switzerland in 1945 documented the increasing frequency of the disease in young patients and cited numerous European references to Crohn's disease. F.N. Silverman[422] of Cincinnati (1966) reviewing 14 children with Crohn's disease (8 male, 6 female) emphasized the alerting clinical features: "children with atypical appendicitis, pyrexia of undetermined origin, growth failure, recurrent abdominal pain and anorexia nervosa." Koop et al.[423] of the United States in 1947 reported a cicatrizing enterocolitis in a newborn involving the entire small intestine and colon. Walter and Chaffin[424] (University of Southern California, Los Angeles) in 1957 reported two cases of apparent segmental enteritis in infancy: one in a newborn female who was operated upon ten hours after birth, disclosing acute inflammation of the distal ileum and the second, in a baby whose symptom of gastrointestinal bleeding began at the age of one month and who was operated upon at the age of three months. A second operation disclosed segmental inflammation of the mid-ileum, fistula formation, skip areas of disease, and "typical" histologic findings.

As with ulcerative colitis, the clinical spectrum of Crohn's disease steadily expanded. In 1948 Kirsner, Owens and Humphreys[425] described regional enteritis in father and son with exactly the same disease in the terminal ileum. Ginzburg and Oppenheimer[426] directed attention to the urological complications in regional ileitis, expanded later by F. Gross of Stuttgart, Germany[427] (1959). J.R. Ross[428] (1949) of the Lahey Clinic, Boston described in sequence cicatrizing ulcerative enteritis, colitis and gastritis in a 21-year-old white female, undergoing multiple operations including: resections of terminal ileum (38 inches of terminal ileum), an abdominoperineal resection and partial (50%) gastric resection. Another instance of Crohn's disease of the stomach was reported by Martin and Carr of London.[429] In 1950, Franklin and Taylor[430] of London described Crohn's disease involvement of the esophagus. The 1951 review of 40

patients with regional enteritis by G.F. Dashiell, J.B. Kirsner et al.[431] (Chicago) emphasized the pathophysiology of the disease. Of the four deaths, two resulted from complications of the disease, one patient died of coronary occlusion, and the fourth death was a suicide. In 1954 Crohn and Janowitz,[432] reflecting on the status of regional enteritis after 20 years, emphasized the vulnerability of the entire small intestine. One year later, Janowitz,[433] reviewing current problems of regional enteritis, implicated "materials in the intestinal content in the recurrences gaining access via the ileal lymphatics." This aspect was reviewed comprehensively in 1998.[434]

In 1956 Zetzel[435] of Boston, in a survey of 69 publications, updated the clinical status of regional enteritis and current etiologic concepts. Chapin, Scudamore, Baggenstoss, and Bargen[436] in 1956 enumerated the complications of regional enteritis at autopsy in 39 patients, including peritonitis (49%), fatty liver (51%), glomerulitis (33%) and vascular thrombosis (21%). Ford and Vallis[437] described the clinical course of the arthritis associated with ulcerative colitis and with regional ileitis. Other complications reported during this time included perforation of the bowel,[438] the only case of generalized amyloidosis[439] in a 33-year-old female with regional enteritis of the terminal ileum seen at Mt. Sinai Hospital. The recognition of carcinoma of the jejunum in a patient with regional ileitis[440] was followed by the comprehensive study of carcinoma complicating Crohn's disease by Weedon et al., comprising 440 patients with an impressive 92% followup.[441] L. Falla-Alvarez (a former student of H.L. Bockus in Philadelphia) and R. Albacete[442] in 1958 recorded their experience with 20 patients with regional enteritis in Cuba, observed between 1950 and 1957, illustrating the importance of physician awareness acquired at a major medical center in facilitating recognition of the disease in their home countries yet unaware of the problem. A second report of regional enteritis in Cuba appeared in 1966.[443] Seeking a reliable laboratory index of disease activity in IBD, W.T. Cooke et al.[444] of Birmingham, England, in 1958 proposed the measurement of seromucoids as an index of disease activity in regional enteritis, but this test was not adopted generally.

General Eisenhower's intestinal obstruction secondary to an old regional enteritis (thickened, narrowed terminal ileum), managed successfully by an intestinal bypass operation (ileotransverse colostomy without bowel resection) in 1956,[445,446] stimulated interest in Crohn's disease, particularly in the United States, and encouraged a onetime modest ($100,000) multiple center outlay of research funds from the National Institutes of

Health. Eisenhower died in 1969 and autopsy demonstrated a thick-walled, fibrotic "burned-out" regional enteritis, unchanged since the bypass procedure 13 years earlier. The prevailing surgical operation for Crohn's disease for many years had been extensive intestinal resection (guided by multiple intestinal biopsies to ensure the absence of any histologic evidence of visible Crohn's disease at the resection margins) and intestinal re-anastomosis, in a futile effort to eliminate disease, with serious physiologic consequences (short bowel syndrome). The frequent recurrence of disease after bowel resection and re-anastomosis as noted by D.J. Fone,[447] among many others, and the favorable outcome of Eisenhower's intestinal bypass operation encouraged a short trial of the intestinal bypass procedure, soon discontinued because of concern with the associated bacterial (anaerobic) overgrowth in the isolated bypassed segment and the associated hazard of intestinal carcinoma.

In time, Crohn's disease was identified in virtually all areas of the gastrointestinal tract from mouth to anus and elsewhere in the body. Crohn's-type lesions were observed in the mouth,[448] skin,[449] the umbilicus,[450] bone,[451] muscles, and lungs.[452] Involvement of the mouth in Crohn's disease attracted considerable attention in the 1970s. Basu, Asquith, Thompson and Cooke[453] of Birmingham, England found decreased production of salivary IgA in Crohn's patients with active Crohn's disease. T. Lehner[454] of Guy's Hospital, London, extensively reviewed the problem of oral ulceration, comparing Crohn's disease with Behçet's syndrome; a viral infection with clinical similarities to Crohn's disease. In a letter to the editor, Matthews et al.,[455] (England) utilizing buccal biopsies, noted that "some patients with Crohn's disease produced antibodies to perinuclear components in buccal mucosal epithelial cells." In 1969, Present, Rabinowitz, Banks and Janowitz[456] described the occasionally unrecognized complication of obstructive hydronephrosis resulting from envelopment of the lower end of the ureters in the intestinal inflammation. Heaton and Rich[457] of Bristol, England (1969) described the altered bile salt metabolism and the pathophysiology underlying the frequency of gallstones in patients with regional ileitis. Smith, Fromm and Hoffman[458] in 1972 reviewed the pathophysiology of acquired hyperoxaluria and nephrolithiasis in small intestinal disease.

In 1963, J. Kyle et al.[381] of Aberdeen, Scotland investigated possible causes of regional enteritis in a study of 54 patients. In 15% of cases, the disease did not begin until after the age of 50. None of the patients was Jewish. Kyle already had noticed a rising incidence of the disease during the latter years of his study. The series included one instance of familial

incidence (mother and daughter) and one patient in whom abdominal trauma preceded the occurrence of Crohn's disease. In 30 patients, intestinal tissue cultures and serum antibody studies for adenovirus and Coxsackie B were indecisive. Intestinal autoantibodies (immunofluorescent and double diffusion in agar techniques) were not found.

In 1966 Gjone, Orning and Myren of Oslo, Norway[459] soon noted the increasing prevalence of Crohn's disease in Norway, a trend soon evident in other Scandinavian countries and continuing today. Clinical reports from Norway[460] and Northern Ireland,[461] added to the increasing interest in IBD. A workshop (Leiden, Holland), focusing solely on Crohn's disease therapy,[462] included 300 references published during the 1960s and 1970s. A major United States Cooperative Crohn's Disease Study during the 1970s examined various clinical parameters of the disease and developed a Crohn's disease activity index (CDAI), often utilized today in the evaluation of drug therapy.[463–465]

CROHN'S DISEASE OF THE COLON – DELAYED RECOGNITION

Despite early accounts of Crohn's-like inflammatory lesions in the colon, the reports of Dalziel in 1913, Moschowitz and Wilensky in 1923 and 1927 describing "non-specific granulomatous lesions" in both the small and large intestine, a right-sided colitis by Bargen and Weber[466] (1930) and case reports from Mt. Sinai Hospital, New York by R. Colp,[467]and by Crohn and A.A. Berg[468] (1938) for reasons still unclear, the concept of a "Crohn's colitis" was difficult to accept in the United States. The 1930 Bargen-Weber paper described 23 patients with "regional migrating colitis." The sole available method of diagnosis was the single contrast barium examination of the colon. Review of that report revealed (understandably) poor quality X-ray views, identifying only the most pronounced changes in the colon; identifiable today as advanced Crohn's disease (not ulcerative colitis).

Charles Wells[469] of Liverpool in 1952 differentiated ulcerative colitis from Crohn's colitis and recognized "segmental colitis" as a variant of Crohn's disease. W.T. Cooke and B. Brooke[470] of Birmingham, England (1955), described 11 patients, teenagers and young adults with a "non-infective disorder," "non-specific enterocolitis" affecting the small bowel initially and spreading to the colon. Diarrhea was the predominant symptom. Pathologically, the lesion in the small intestine was confined to the mucosa (multiple small ulcers "differing from Crohn's disease" and "backwash ileitis." In the colon the disease was evident initially in the

H.E. Lockhart-Mummery

right colon and resembled ulcerative colitis except for the right-sided involvement ... "it is different ... from ulcerative colitis and from cicatrizing regional enteritis or colitis."

Brooke[471] conclusively identified "right-sided colitis" as Crohn's disease in 1959. But not until the reports of Morson and H.E. Lockhart-Mummery[472] in 1959 and Cornes and Stecher[473] (1961) was Crohn's colitis finally accepted as a distinct entity in the United States, Great Britain and in Europe. (See also review by R.W. Nevin[493a].) Despite the long-term familiarity with granulomatous intestinal disease at Mt. Sinai Hospital (NY), physicians and surgeons at that institution refused for many years to recognize that regional enteritis could involve the colon. Resected specimens of inflammatory disease of both ileum and colon were consistently reported as regional enteritis of the small bowel and ulcerative colitis respectively.

As early as 1951, radiologist R. Marshak (New York) had noted changes in the colon resembling regional ileitis in some patients with so-called ulcerative colitis. Also, other patients with definite regional ileitis presented radiologically-identical disease in the colon, observations he reported at a meeting of the Inter-American Association of Radiologists

R. Marshak

in 1951. At the 1955 meeting of the American Gastroenterological Association, he described the roentgen differences between ulcerative and granulomatous colitis. The discussants of the paper, however, took the erroneous position that granulomatous colitis was a form of chronic ulcerative colitis. In 1959, Marshak[474] published his findings on granulomatous colitis in a paper entitled "Segmental Colitis" but he too suggested that most of the cases of segmental colonic disease probably were instances of ulcerative colitis. However, in 1962 Marshak,[475] in a major presentation to the Radiological Society of North America, entitled "Granulomatous Disease of the Intestinal Tract (Crohn's Disease)", reviewed his remarkable experience with approximately 8000 cases of regional enteritis and 4000 of granulomatous colitis. The paper included his "10 principles of Crohn's disease." He concluded in part: "The main purpose of this talk is to present an overall perspective of granulomatous disease and provide a stimulus, especially to the younger men, for further study of a disease in which there are so many unsolved problems." Numerous papers in the 1960s and subsequently, dealing with the overlapping findings in ulcerative colitis and Crohn's disease of the colon, outlined differentiating features of ulcerative colitis and Crohn's disease of the colon.[476–479] McGovern and Goulston[480] in 1968 re-emphasized the

Henry D. Janowitz

characteristic histologic features of submucosal fibrosis and prominent lymphoid aggregates.

In addressing the question, Why was the recognition of Crohn's colitis so slow?, Janowitz[481] remarked: "The reasons at the home of the American pioneers I believe I can account for. From the 1920s on, Pathology was king, not only at Mt. Sinai but especially there, where Paul Klemperer, who had just arrived from Vienna was to start his long, distinguished career, and under whom Moschowitz and Wilensky and later Ginzburg and Oppenheimer were to work. The central dogma firmly held by the pathologist Dr. Otani of Klemperer's department was that the ileocecal valve was more than a landmark of separation. It was a virtual Mason–Dixon line. In the north, from the duodenum to the ileum occurred regional enteritis. To the south occurred ulcerative colitis and never the twain were to meet or mingle. This perspective determined the attitude through which inflammatory bowel disease was viewed at that time. So fixed was this widely held point of view that these were two geographically as well as nosologically different diseases, that the idea that Crohn's ileitis could occur in the colon was hard to accept by the original Mt. Sinai workers, especially Crohn himself. The tidiness of the original separation

also played its part in the stereotyping of clinical perception. If the hold was so strong at the home of Crohn, Ginzburg and Oppenheimer, it is not difficult to see why others on the American side of the Atlantic failed to accept what had been under their eyes for at least a generation." Following the acceptance of Crohn's disease of the colon as a valid entity, its differentiation from nonspecific ulcerative colitis became an important clinical challenge in 10 to 15% with IBD of the colon. In 1975 Price and Morson of St. Marks Hospital[482] and Kirsner[483] each published helpful differentiating features of Crohn's colitis and ulcerative colitis.

EARLY PATHOLOGY OF CROHN'S DISEASE

In 1938 Coffey[484] (Mayo Clinic) emphasized the early principal anatomic features of Crohn's disease as: subacute or chronic granulomatous inflammation, the tendency to stenosis of the bowel, the fistula formation and the absence of tuberculosis. In 1939 G. Hadfield[485] of St. Bartholomew Hospital, London, in a study of 20 cases of regional ileitis, noting "obstructive lymphedema" and lymphoid hyperplasia in the intestinal submucosa, had suggested "lymphadenoid hyperplasia with the formation of non-caseating giant cell systems in the submucosa" and also in the regional lymph nodes as the earliest and possibly the "specific" histological lesion of regional enteritis. Hadfield et al. concluded: "From the purely histological point of view ... the appearance, evolution and retrogression of the giant cell systems of regional ileitis more closely resemble the tissue reaction of Boeck's sarcoidosis than of tuberculosis infection."[486] Testing this hypothesis, Kveim skin tests for sarcoidosis later were negative in patients with regional enteritis.

The production of granulomas by antigen-antibody complexes[487,488] in 1966 and 1969 stimulated interest in possible contributory immune mechanisms. In the 1970s the etiologic significance of the granuloma in Crohn's disease was unclear, although the microgranuloma was considered an early indication of Crohn's disease.[489] Chambers and Morson[490] in 1979 stated, "It (the granuloma) is generally assumed to represent a response to the aetiological agent (for example, a 'poorly soluble antigenic agent') ... It is conceivable that it follows mucosal ulceration with resulting penetration of bowel contents into tissues ..." although "granulomas are often seen in non-ulcerated bowel wall and no luminal debris can be identified." The early emphasis upon the possible etiologic importance of the intestinal granulomas generated modest interest in the nature of the granuloma and in conditions associated with granuloma formation.

Though differing in some features, as originally noted by Lartigau in 1901, the association of granulomas with tuberculosis, actinomycosis, schistosomiasis, sarcoid, and histoplasmosis, as well as foreign body granulomas (talc, lipid, silica, mercury and beryllium) actually diminished their diagnostic usefulness in Crohn's disease. Furthermore, Whitehead[491] of Australia demonstrated microgranulomas and giant cell reactions also in ulcerative colitis. Kirsner also had observed granulomas in experimental injury of the bowel. In 1973 Aaronson and Spiro[492] (Yale University) speculated on a possible role for mercury in inflammatory bowel disease and in 1987 P.O. Ganrot[493] (Orebro, Sweden) proposed aluminum as a "possible etiologic agent" in Crohn's disease, but neither suggestion attracted attention. In 1992 J.V. Weinstock,[494] University of Iowa, Iowa City, authoritatively reviewed the subject of the granuloma and Crohn's disease.

The 1948 study of 120 cases and the comprehensive literature review by S. Warren and S.C. Sommers[495] of the New England Deaconess Hospital, Boston had emphasized the cicatrizing nature of the tissue reaction, in addition to the "granulomatous response in the intestine." Giant cell systems, including giant cell inclusions, were present in lymph nodes even when not present in the intestine. As stated by Warren and Sommers: "A progressive sclerosing granulomatous lymphangitis, probably as a reaction to an irritative lipid substance," is of interest in relation to the later implication of lipids in Crohn's disease.[496]

H. Rappaport et al.,[497] at the U.S. Armed Forces Institute of Pathology in Washington D.C., in 1951 reviewed 100 cases, including 85 bowel resections and 15 autopsies. In 72 instances, sections from mesenteric lymph nodes and in 35, appendices were available for study. The "tubercle-like granuloma observed in about half of the group, differed from foreign body granulomas and from the sarcoid lesion. Lymphedema and lymphangiectasis were common." Ulceration was not the primary lesion in regional enteritis but was preceded by lymphoid hyperplasia. Rappaport et al. were able to histologically differentiate regional enteritis from chronic ulcerative colitis. S. Otani[498] of Mt. Sinai Hospital (1955) and R. Whitehead of Australia[499] (1980) each provided detailed reviews of the pathology of regional enteritis and regional enterocolitis. Otani concluded "since the pathological picture of the colonic lesions is so identical with that of regional enteritis, it is logical to assume that the simultaneous association of regional ileitis and colitis should not be interpreted as a mere coincidence, since they may have a common etiological factor."

In 1954 Warren and Sommers,[187] comparing the pathology of ulcerative colitis and regional ileitis, reaffirmed: "The histopathology of regional ileitis would suggest a reaction to irritative lipid substances. It appears possibly to represent a by-product of some biochemical abnormality of lipid absorption in the intestine," but this possibility was not pursued.

In 1955 Davis, Dockerty and Mayo[500] examined the myenteric plexus of the ileum in 24 patients with regional enteritis (with allowance for thickening and shrinkage of tissue) and, as in ulcerative colitis, found a threefold increase in the number of ganglion cells, compared to controls. The increased ganglion cells were present in adjacent, apparently normal bowel as well as in diseased areas. The only explanation offered, as in the ulcerative colitis study, was "the stimulus of ulceration and increased function to the growth of small undeveloped nerve cells."

Binney[501] observed endarteritis obliterans and perivascular infiltration of plasma cells in the small intestine but made no etiologic inferences. Interestingly, Warren and Sommers[187] had observed "inflammatory necrosis" of arteries and veins also in ulcerative colitis. B.C. Morson[502] for many years had identified foci of vasculitis (arteritis) in surgically resected and in biopsy tissue of Crohn's disease and "I often wondered about the importance of this lesion." Recent interest in a possible focal "granulomatous" mesenteric vasculitis involving mucosal and submucosal vessels, inducing focal ischemic damage, and mini-infarctions of the intestine related to the measles virus as an explanation for the focal distribution of Crohn's disease[503] has not received strong support. Also, the specificity of "focal lesions" (CD) may be in question if "multifocal colitis" also characterizes colitis of infectious origin[504] and allergic proctocolitis in infants.

In 1961, R.W. Ammann (Zurich, Switzerland) and H.L. Bockus[505] (Graduate Hospital, Philadelphia), emphasizing "immunologically-induced edema" as the earliest histologic lesion, re-examined surgical specimens from 40 patients with regional enteritis. In the proximal preulcerous segments, the changes (edema, mucosal distortion, inflammatory reaction of the lamina propria with PAS-positive macrocytes and 'Brunner's glands') were attributed to an obstructive lymphedema, similar to the changes observed in experimental chylous obstruction. Granulomatous changes within or around lymph vessels were noted frequently. Similar alterations had been recorded by Schepers[506] in 1945. In 1964 T.K. Shnitka[507] of Edmonton, Alberta, Canada, like others, emphasized lymphangiectasis, lymphedema, lymphoid hyperplasia and granulomatous inflammation of the submucosal and subserosal layers of the

intestine. Chronic ulcerative colitis, on the other hand, began in the mucosa with "crypt abscesses" and progressed transmurally only in its later stages.

In the absence of acceptable endoscopic biopsy technology, the "early" pathologic studies of Crohn's disease had dealt with advanced stages of the disease.[508] In 1972 B.C. Morson[509] of London identified the "earliest macroscopic lesion of Crohn's disease as the tiny aphthoid ulceration (micro-erosion)," as had been noted by B. Brooke in 1953.[134] Poulsen et al.[510] of Copenhagen, Denmark identified microerosions often associated with granulomas in rectal biopsies in patients with Crohn's disease. In 1980 the aphthoid ulcer was located by Rickert and Carter of Livingston, New Jersey precisely over the special membranous M cell[511] situated in the epithelium overlying lymphoid follicles in Peyer's patches, a finding of considerable, as yet incompletely evaluated pathogenetic importance. The M cell, a membranous cell type that allows molecules and microorganisms to reach the organized mucosa-associated lymphoid tissue, only now is attracting increased scientific attention. (See later.)

Morson[502] in the 1960s and 1970s had summarized the gross pathological features of Crohn's disease, including thickened adherent mesentery, thickened small bowel, enteric fistulas, intestinal narrowing, aphthous ulcers, and linear serpiginous ulcers, cobblestone appearing mucosa, and the asymmetrical focal distribution of the disease. Distinctive histologic findings included focal lesions, transmural inflammation, dilated submucosal lymphatics, prominent lymphoid aggregates, knife-like fissuring ulcerations, granulomas, hypertrophy of the muscular layer and neural hyperplasia. The diagnostic emphasis histopathologically was upon a collection of features, rather than a single abnormality (focal submucosal involvement, dilated lymphatics, lymphoid prominence, non-tuberculous granuloma, vertical fissures). None of these features, in fact, was an early manifestation of a disease that probably also involves the intestinal mucosa.

The development of gastrointestinal endoscopy,[512] including the fiber-optic colonoscope and the associated improvements in biopsy technology during the 1950s provided access to intestinal tissue at earlier stages of IBD. Increased knowledge of intestinal epithelial function and the response to injury provided new insights into the nature of the IBD tissue reaction.[513]

ELECTRON MICROSCOPY – CROHN'S DISEASE

In a 1971 electron microscopic study, Aluwihare,[514,515] St. Marks Hospital, London, examined colon tissue obtained at operation or biopsy specimens from the colon and rectum of patients with Crohn's disease, fixed in 1% osmium tetroxide. Where the bowel was not ulcerated, the epithelial cells appeared normal, as did their microvilli. In contrast to ulcerative colitis, the epithelial cells, initially intact, appeared smaller, with stunted microvilli. There was mild edema between the cells but the underlying basement membrane and collagen were intact. Numerous plasma cells and lymphocytes were present in the broadened lamina propria. The lymphocytes contained prominent nucleoli, as seen in immunologically-stimulated lymphocytes. Most of the nerve and muscle cells and the blood vessels appeared normal. The epithelioid cells in the granulomas contained large nuclei with finely dispersed chromatin and a clear-cut nucleolus. The margins between the epithelioid cells were undulating and interdigitating, without a true basement membrane. Towards the periphery of a granuloma, the endoplasmic reticulum of the epithelioid cells appeared coarse in texture. Nearer the center, they contained vacuoles, representing metabolic activity. Electron microscopic histochemistry demonstrated acid phosphatase, an important lysosomal enzyme in the clear vesicles present in the epithelioid cells. Clusters of bacteria were seen in the deep layers of the colon. Organisms were not seen in similar sites of normal colon. Aluwihare regarded the changes in the lymphocytes, plasma cells and epithelioid cells as compatible with "some immunological reaction," but secondary manifestations were not excluded.

Ranlov, Nielsen and Wanstrup[516] (Copenhagen) in 1972 reported electron microscopic findings in surgical tissues from two patients with "advanced Crohn's disease of the ileum" (one male 26, one female 24) and were impressed with the many small and large lymphocytes, plasma cells, epithelioid cell granulomas and unusually large number of mast cells, "attributable to cell-mediated immune mechanisms." Microorganisms were not seen. In 1974 Siemers and Dobbins[517] of San Diego, California published a light and electron microscopy study of the Meissner submucosal plexus in normal colon and the colon of patients with Crohn's disease. Ganglion cells of the plexus in Crohn's disease appeared normal. Minor changes included axon dilatation, increased numbers of neurofilaments and penetration of nerve fibers by plasma cells and mast cells. There was no hypertrophy of ganglion cells but centrioles in ganglion cells were prominent. The authors speculated on a process of "mitotic division

of otherwise normal neurons." Although the emphasis in Crohn's disease traditionally has been upon submucosal and transmural disease, Dourmashkin et al.[518] (England) in 1981 on electron microscopy noted "early epithelial lesions."

The axonal necrosis of autonomic nerve fibers and ganglion cells in Crohn's disease, observed at electron microscopy by A. Dvorak (Beth Israel Hospital, Boston),[519–521] and the earlier observation of mast cell hyperplasia in the ileum of Crohn's disease,[522] presumably consequences of the inflammatory reaction (or perhaps "the ultrastructural correlate of an autonomic neuropathy") remain unexplained. Additional findings such as mast cell degranulation, release of basic protein-containing eosinophilic granules[523] (primarily affecting autonomic nervous system axons), myofibroblast proliferation, increased numbers of polymorphonuclear leukocytes, lymphocytes, eosinophils, macrophages, basophils, and Paneth's granular cells and alterations in epithelial cells reflected the complexity of the CD tissue reaction.

In 1981, Otto (Hamburg, Germany) and Gebbers (Lucerne, Switzerland)[524] described immunohisto- and ultracytochemical studies on surgical and biopsy specimens from 27 patients with Crohn's disease of the ileum or colon. Control specimens were obtained from 16 patients with nonspecific proctitis or neoplastic disorders of the cecum or rectum. The initial lesions in Crohn's disease were associated with a "typical humoral immune response." In non-ulcerated mucosa a uniform increase of IgA-, IgG- and IgM-cells was found, whereas disproportional increases of IgG- and IgE-cells were observed in ulcerated mucosa. The IgE-cell multiplication in ulcerated areas suggested a local hypersensitivity reaction. Macrophages and granulocytes contained IgG, also present in multinucleated giant cells. The granulomas contained extracellular IgG, acid phosphatase and peroxidase. The finding of "potentially harmful" extracellular lysosomal enzymes was attributed to "autoimmune phenomena." Micro-ulcerations of the dome epithelium of hyperplastic Peyer's patches were an early lesion through which luminal antigens gained uncontrolled access to Peyer's patches. C1q or C3 bound to epithelial or vascular basement membranes were not detected and no electron dense deposits were found. Viral particles or bacteria were not demonstrated by electron microscopy.

Later studies by Marin et al.[525] of New York, utilizing freeze fracture electron microscopy, demonstrated a variety of changes in the ileal mucosa of Crohn's disease, including large lysosomal inclusions in epithelial cells, alterations in villi, dilated goblet cells and pinpoint

aphthoid ulcers and in the involved colonic mucosa, loss of the normal mucosal architecture, changes thought to represent secondary tissue reactions. Marin et al.[526] were intrigued by the fusion of "limiting and inclusion granule membranes" within the epithelial cells in CD and considered their pathogenetic significance. In 1995 Nagel et al.[527] of Hannover, Germany, in a scanning-electron-microscopic study of surgically-resected bowel from 29 patients with Crohn's disease and 11 control subjects, correlated a triad of early lesions: mucosal architectural alteration, epithelial bridge formation and goblet cell hyperplasia with the frequent recurrences of CD. These observations extended the 1976 findings of Goodman, Skinner and Truelove,[528] who, with light microscopy, had noted more diffuse involvement of the small intestine than was apparent visually. In considering the "early" vs. late pathologic studies of IBD, the 1972 comments by James Kyle are relevant 30 years later. "Probably too much attention has been paid in the past to the end-product (and I would include the granuloma). All routine and most research pathology studies tend to concentrate on the worst affected part of the intestine ... but this type of examination is most unlikely to throw much new light on the early stages of the disease when aetiological clues are more likely to be discerned," (as in early colonoscopic biopsies). The issue of "early" and "late" Crohn's disease continues to be debated by physicians, surgeons and pathologists; in part because of the difficulty in assigning "time-related labels" (early, late) to the complex biologic phenomena characterizing CD.

ORIGIN OF EPONYM OF CROHN'S DISEASE

Many terms have been applied to the disorder originally labelled terminal ileitis: regional enteritis, chronic cicatrizing enteritis, nonspecific granuloma of the intestine, hyperplastic ileitis, chronic ulcerative ileitis, enteritis phlegmonosa, ileocolitis, inflammatory pseudo-tumor of the intestine, regional ileitis of the colon and Crohn's colitis. British reports of "granulomatous inflammation" of the small bowel in Great Britain in the 1930s occasionally were referred to as Crohn's disease.[529,530] In the United States, the term Crohn's disease probably was first employed as an eponym by F.I. Harris[334] (1933) in the article "Chronic cicatrizing enteritis of the ileum: Regional ileitis (Crohn)." B.C. Cushway[531] of Chicago in a 1934 case report used the title "Chronic Cicatrizing Enteritis, Regional Ileitis (Crohn)." R.F. Barbour and A.B. Stokes[532] of the Maudsley Hospital, London wrote in 1936: "To this localized condition the name of regional

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enteritis was given, although in America it also became known as Crohn's disease. A.F. Hurst and G.A.M. Lintott[533] (London) in 1937 also referred to Crohn's disease. Physicians in other countries likewise claimed publication priority. Thus, in Poland, this entity was called "Lesniowski–Crohn's disease."[534] (Antoni Lesniowski and his contribution to Regional enteritis [Crohn's Disease]). H.I. Goldstein[295] utilized the term: "Saunders–Abercrombie–Crohn's ileitis," to recognize early British describers of the entity.

To American observers, this entity might justifiably have been designated "CGO disease" to reflect the important contributions of not only B. Crohn but also L. Ginzburg and G. Oppenheimer who provided 12 of the 14 cases in the 1932 JAMA paper. Also Ginzburg was acknowledged by Crohn himself as having studied intestinal granulomas and intestinal inflammatory pseudotumors long before Crohn, justifying Ginzburg's claim for co-designation. The term Crohn–Dalziel disease as suggested by M. Harmer[535] appealed to many, in recognition of Dalziel's significant 1913 paper, including J.F. Fielding[536] and J. Kyle.[537,538] The term "cicatrizing enteritis" proposed by Warren and Sommers, according to Armitage and Wilson,[539] "though a fair term is far from euphonious." "The name Crohn's disease has been adhered to in most cases at this

hospital (Leeds). It avoids confusion, makes no pretense of pathological exactitude, conveys an exact meaning, is easily remembered by students, and pays a well deserved tribute." Apparently unaware of the precise chronological events, the designation of Crohn's disease was endorsed at the 8th International Congress of Gastroenterology in Prague, Czechoslovakia in 1968. Whatever the "labeling" circumstances, the entity today carries the eponym Crohn's disease as the most convenient designation, now sanctioned by worldwide, long-term usage, for an unique inflammatory process involving any part of the gastrointestinal tract, characterized by chronicity, recurrences, and numerous complications.

To the credit of Crohn, Ginzburg, and Oppenheimer is the globally-acknowledged fact that their timely clinical description and subsequent numerous, important contributions, although initially focussed on the terminal ileum, stimulated interest in an emerging worldwide disease. As Brooke, Morson, Truelove, Heller and other IBD observers had suggested in personal communications, "the time (1932) was right" for the description of this disorder and, had the Mt. Sinai group not assembled their paper, others soon would have done so (see also A.H. Aufses[540]).

On the matter of eponyms, the comment of Thomas Lewis[541] in 1944 remains pertinent today: "Diagnosis is a system of more or less accurate guessing, in which the end point achieved is a name. These names applied to disease come to assume the importance of specific entities ... whereas they are, for the most part, no more than insecure and therefore temporary conceptions." Presumably, the Crohn's designation will yield to the etiology of the disease when it is discovered!

EDITORIAL NOTE

With the conclusion of this overview of origins, early discovery and increasing clinical recognition of ulcerative colitis and Crohn's disease, the remainder of this publication is focused on the nature and etiopathogenesis of ulcerative colitis and Crohn's disease. The following sections include: early epidemiology, psychogenic aspects, microbiological possibilities, immune mechanisms, including M cell, epithelial permeability and inflammation, genetic possibilities and a concluding commentary. The early treatment of inflammatory bowel disease is reviewed in the appendix, together with a listing of earlier IBD publications.

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