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Inflammatory Bowel Disease after 1932

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Abstract

The clinical diseases of ulcerative colitis (UC) and Crohn's disease (CD) were defined by 1932 – 1933. After that, the major conceptual developments were the recognition that regional enteritis could clearly involve the colon, and that cancer and toxic megacolon could occur in both CD and UC. In the last half of the 20th century the main thrust of gastroenterology at The Mount Sinai Hospital has been in inflammatory bowel disease (IBD), with contributions to extra-intestinal manifestations, measurement of clinical activity in CD, the natural history of the placebo arm of controlled trials, complications and therapy with corticosteroids, 5-ASA, 6-mercaptopurine, immunomodulators and cyclosporine. Actuarial life tables were introduced for postoperative recurrence and re-operation rates, as well as for quality of life analysis. Two forms of CD were defined, perforating and non-perforating, and the role of the fecal stream was explored in light of the higher risk of recurrence after operations with anastomosis as compared with ileocolostomy. **Key Words:** Inflammatory bowel disease, regional enteritis, ulcerative colitis, Crohn's disease.

THE STUDY OF INFLAMMATORY BOWEL DISEASE (IBD) has a long history at The Mount Sinai Hospital. The preceding section by Hugh Baron documented the path that led to the discovery of the disease we now call Crohn's disease (CD). By 1932 – 1933, the papers of Ginzburg and Oppenheimer (presented before the American Gastroenterological Association), Crohn, Ginzburg and Oppenheimer (before the American Medical Association), and by Ginzburg and Oppenheimer (before the American Surgical Society) had described the entity not only in the ileum, but in the colon as well. With the subsequent description of cecal involvement (1) and the recognition of perineal disease (2), the basic clinical and pathologic features of this still enigmatic, serious, chronic and lifelong disorder were in place.

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The 1930s to the 1950s

One would have expected an explosion of interest and study at the institution where it was discovered. Crohn continued to collect his series of cases, and with John Garlock, his surgeon, reported the results of resection (3, 4). In 1939, Ginzburg and his colleagues noted the surprising effects of bypassing the ileal lesion by diversion of the intestinal fecal stream (5). However, gastroenterologists at The Mount Sinai Hospital did not focus intensely on CD. This was especially so in the question of colonic involvement. Bargen and Weber (6) and Crohn and Berg (7), in the 1930s, called attention to "right-sided colitis," and several years later, in 1952, Wells (8) recognized "segmental colitis" as a variety of CD, separating it from ulcerative colitis (UC). Indeed, most American gastroenterologists remained indifferent as to this important feature of CD. This held true not only for Crohn himself but for the other gastroenterologists at Mount Sinai, except for Richard Marshak, the radiologist, who firmly maintained and lectured on the fact that regional enteritis could clearly involve the colon (9).

Two factors were probably important in causing this delayed recognition of Crohn's colitis. First, the focus of clinicians such as Asher Winkelstein, and radiologists such as Bernard Wolf, was directed to peptic ulcer disease and hiatal hernia. The Gastrointestinal Research Laboratory, directed by Franklin Hollander and sponsored by the surgical departments at The Mount Sinai Hospital, especially that headed by Ralph Colp, was centered on ulcer disease, acid secretion, vagotomy, and the mucus barrier of the stomach (see Mt Sinai J Med 2000; 67:14–40). Additionally, David Dreiling had started his work on the pancreas in this laboratory (see Mt Sinai J Med 2000; 67:68–75).

Perhaps more important was the strong stand that the pathologist, Sadao Otani, had taken. He had insisted that the ileocecal valve separated regional ileitis from ulcerative colitis. It was the publication by Lockhart-Mummery and Morson (10) and the worldwide acceptance of their concept of CD of the colon that really opened the floodgate at this institution.

Some indication of the climate of opinion at Mount Sinai during this interval may be seen in the fact that, when I arrived as an intern in November 1939, seven years following the seminal papers, the general clinical attitude was tinged with slightly skeptical amusement at Crohn's interest in regional enteritis. When I returned again in 1950, after World War II and a period of research elsewhere, the climate had changed. Senior clinicians, and especially radiologists, were intensely interested in IBD. Marshak meticulously described the evolution of regional enteritis as it appeared in serial x-ray films during the life of a patient (11).

Interest too was centered on ulcerative colitis, focused, in particular, on toxic dilation of the colon. R.H. Marshak, L.J. Lester, and A.I. Friedman (12) had described the megacolon of ulcerative colitis and coined the term "toxic megacolon" and Greenstein et al. (13) followed up with a study of the outcome of toxic dilation of the colon in UC and CD. Even the problem of cancer in inflammatory bowel disease had been recognized. Crohn had described the first case of cancer of the colon in UC in 1925 (14). In 1956, Ginzburg et al. (15), described the first case of carcinoma (of the jejunum) in regional enteritis.

From the 1960s

The formal organization of gastroenterology at The Mount Sinai Hospital in 1958, with the founding of the first separate division within the Department of Medicine, marked the beginning of more intense interest in many aspects of inflammatory bowel disease. Contributions by those in Surgery, Radiology and Immunology are detailed in this issue, by Aufses, Maklansky and Mayer. By the end of the 1960s, an informal group of clinical investigators was slowly forming. Present, Korelitz, and myself, from the Division of Gastroenterology, were later joined by Sachar and Meyers. The combined cooperation of the surgeons Aufses, Gelernt, and Greenstein played an important part. Greenstein had begun to assemble a database of all patients with IBD (UC and CD) seen at the hospital, making an especially important contribution. The return of Lloyd Mayer to The Mount Sinai Hospital, after a brilliant stint at the Rockefeller Institute in the laboratory of Henry Kunkel, further strengthened the collaborative team in immunology, while a younger generation of graduating fellows who became involved with this group included Lichtiger and Kornbluth. These contributions are now reviewed.

The Natural History and Complications of IBD

The first American paper on Crohn's colitis in the post-Lockhart-Mummery and Morson era appeared in *The New England Journal of Medicine* in 1963, a joint paper of Lindner (a fellow in Gastroenterology), Marshak, Wolf (Radiology), and myself (16). Articles on "granulomatous colitis," the term we used at The Mount Sinai Hospital to avoid offending Leon Ginzburg, appeared in *JAMA* in 1965 (17). Others were then published in rapid succession in the *Annual Review of Medicine* of 1966 on ileocolitis (18) and in *Gut* in 1966, with Marshak as a co-author (19).

Extra-intestinal Manifestations of IBD

The long-standing interest in these manifestations culminated in 1976 in the paper most frequently cited in the literature, which was from this division (20). It offered for the first time a classification into the categories of "colitis associated," "results of small bowel pathology," and "an immunological group." This classification helped sort out the protean manifestations associated with inflammatory disease activity (especially in the colon) from those unrelated to disease activity.

Measurement of Clinical Activity in CD

The measurement and quantification of disease activity in CD represent a continuing problem. A wide range of laboratory tests, including

labeled colonic or fecal leukocytes, are widely used by different clinical investigators. Following the report of Thomas et al. (21) on the use of random stool specimen concentrations of fecal α-1-antitrypsin in children with CD, we reported that this technique was a useful measure of clinical activity of CD in ileum and colon in adults (22) and the effects of therapy and anatomical extremes in this disorder (23). Other studies indicated that the erythrocyte sedimentation rate (ESR) was also a useful indicator of disease activity, but primarily in extensive colonic disease as opposed to small bowel involvement (24, 25).

Natural History of Inflammatory Bowel Disease

More recently, our interest in the natural history of IBD led to the novel suggestion that we look at the "placebo arm" of published trials. Since almost all patients described in the literature with these diseases have been treated with a variety of drugs, we used the placebo arm of controlled trials as a measure of the natural history of CD and UC. This approach, focused on the placebo response in IBD both in Crohn's disease (26) and ulcerative colitis (27), has markedly affected evaluations of results of current therapeutic trends.

Complications of Inflammatory Bowel Disease

The complications of IBD have been explored with an avid and active interest on the part of the division of gastroenterology.

Cancer in IBD

Cancer in IBD is fully discussed by Adrian Greenstein (see this issue). Here we call attention to the early recognition of cancer risk in Crohn's disease, not only in bypassed loops (28, 29), but also in long-standing Crohn's disease of unoperated small bowel and colon (30–33).

Toxic Dilation of the Colon

An early interest in toxic dilation of the colon was sparked by Marshak (34), and again in 1985, in a paper by Greenstein, Sachar and others (13), devoted to the outcome of toxic dilation in patients with these diseases. In 1980, pneumomediastinum was described as a perforating complication of toxic dilation (35) and in 1988 Present reported on his therapeutic use of "rolling" of the patients with toxic megacolon (36).

Obstructing Hydronephrosis

The discussion of renal disease in IBD began at The Mount Sinai Hospital with the report by Deren, Porush, Levitt and Khilnani on the study of kidney stones as a complication of UC and CD (37). The important and, up to then, frequently unrecognized obstructive hydronephrosis complication of Crohn's disease was detailed by Present, Rabinowitz, Banks and Janowitz (38).

Suppurative pylephlebitis with liver abscess was recorded early in 1962 (39).

Blood Disorders

Autoimmune hemolytic anemia was described in some detail along with an analysis and evaluation of its current therapy in 1979 (40). Cryoglobulinemia with skin involvement, including gangrene of fingers and toes, was described early in 1979 and in 1981 (41, 42). The association of acute myelogenous leukemia with ulcerative colitis was first correlated by Fabry, Janowitz and Sachar with the considerable amount of previous x-ray exposure in these patients (43). Additional reports from other institutions then followed.

Pyoderma Gangrenosum

Pyoderma and trauma to the upper extremities were reported in 1981 as being associated with IBD, their existence having been known to dermatologists but apparently not recognized by gastroenterologists (44). An important study of the outcome in patients with pyoderma treated by colectomy appeared in 1983 (45). It showed that patients with active colitis healed promptly, while patients with less active disease required up to one year to heal, although all did heal eventually.

Amyloid

Amyloidosis, especially renal amyloidosis, has been of continued interest to the division. One of the earliest series (five cases of amyloidosis) in regional enteritis was published in 1960 (46) and the 50-year experience with 25 patients was recently brought up to date in *Medicine* (47) in 1992. The first cases of renal amyloidosis with severe proteinuria associated with inflammatory disease treated successfully with colchicine were reported by Meyers, Janowitz, Gumaste and other colleagues (48).

"Metastatic" CD

Along with cutaneous manifestations of CD patients, an early interest in "metastatic" CD was reported from the gastroenterology division and the Department of Dermatology in 1984 (49).

Pancreatitis

A very early report by Meyers and colleagues from the division stressed the curious association of acute pancreatitis with active Crohn's disease (50). This may be related to the recent report of elevated titers of pancreatic tissue antibodies in Crohn's disease (51).

Central Nervous System Involvement

Early on, Silverstein and Present called attention to the tragic situation of central nervous system catastrophes, in the form of cerebrovascular occlusion, in some young patients with CD (52).

Pregnancy and IBD

Mount Sinai gastroenterologists have had a very long and active interest in the effects of pregnancy on the course of IBD patients and on the outcome of the fetus, beginning with the early paper of Crohn, Yarnis and Korelitz (53). Korelitz has continued to review his and his colleagues' experiences in this area, reporting his data from time to time. His review on the effects of sulfasalazine and steroids on pregnancy and the fetus has given important reassurance to gastroenterologists worldwide of these drugs' safety (54). Present and co-workers will soon report on the largest series of pregnant women who have conceived successfully while on 6-mercaptopurine; this will help resolve the question of its safety.

Therapeutic Contributions

The division has made important contributions to the medical therapy in IBD in several areas.

ACTH versus Hydrocortisone

The introduction of steroid therapy in 1954 by Truelove and Witts (55) focused clinical attention for a long time on the intravenous administration of ACTH and the use of steroids and the routes by which they were administered. The publication by Meyers, Sachar, Goldberg and Janowitz (56), comparing the clinical responses to intravenous ACTH and hydrocortisone of patients sick with ulcerative colitis, showed that the response depended on patients' recent experiences with steroids. ACTH was superior to hydrocortisone for patients who had no recent exposure to prednisone. Resisted at first, the concept seems now generally accepted for ulcerative colitis.

Mesalamine

An early paper by Meyers, Sachar and Janowitz, joined by Present (57), showed the efficacy of olsalazine (Dipentum) in ulcerative colitis in a prospective, randomized, double-blind, dose-ranging, placebo-controlled trial. This study helped to establish this variant of 5-ASA for patients allergic to or intolerant of sulphasalazine (Azulfidine).

Immunomodulators

Although azathioprine had been used since 1964 for the treatment of UC, fear of malignancy and "cure" by colectomy, with a reasonably normal lifestyle with the Brooke ileostomy had led to its disappearance from the therapeutic armamentarium for chronic ulcerative colitis. There can be no doubt that the introduction of 6-mercaptopurine by Present, Korelitz, Wisch, Glass, Sachar, and Pasternack for the treatment of Crohn's disease in a long-term, randomized, double-blind study (58) marked an important turning point in the history of treatment for CD. The detailed story of the slow reception, published controversy and ultimate acceptance of this form of therapy (59) is given by Korelitz and Present (see this issue). Its triumphant story is to be attributed to the persistence and determination of the investigators, and their careful follow-up study on toxicity and malignant potential. Its worldwide acceptance is a feather in the cap of this division.

Cyclosporine

Although cyclosporine has not proved to be very effective in CD, its introduction for severe ulcerative colitis refractory to steroid therapy by Lichtiger, Present, Kornbluth and co-workers in 1994 signaled another important new modality for these seriously ill patients facing urgent colectomy (60). Careful follow-up studies of Kornbluth and others on toxicity and quality of the long-term results have already furnished us with valuable information on its long-term benefits and risks (61, 62).

Omega 3 Fatty Acids

Although the real place of fish oil omega 3 fatty acids as an anti-inflammatory agent and as a treatment in UC and CD is yet to be defined, interest in this modality was shown by a very early open trial for UC in this division (63).

Mount Sinai Gastroenterology and Its Interaction with Patients

At present, with our intense interest in the effects of IBD and its therapy on the lives of our patients, it is important to remember Mount Sinai's contributions which go back a long time. One of the earliest papers on the "quality of life" with IBD was a publication on the study of the quality of life after surgery for CD in the form of psychosocial assessment, published twenty years ago (64). More recently, direct comparisons are being made between medical and surgical treatment, for their quality of life outcomes (65).

The formation of the National Foundation for Ileitis and Colitis (NFIC), now known as the Crohn's and Colitis Foundation of America (CCFA), at The Mount Sinai Hospital, was an important step in organizing the partnership of the scientific community with the lay public, especially the families of patients with IBD 33 years ago. Present was its first Research Fellow, and was succeeded by Sachar. Its National Scientific Advisory Committee was chaired first by Janowitz (1969 – 1979) and later by a Mount Sinai alumnus, Lenox Hill's Korelitz (1981 – 1984). This partnership now raises millions of dollars for research, patient information books (edited by Present and colleagues) and physician education, an amount far greater than the NIH budget for IBD.

The Ileostomy Society, organized at Mount Sinai by Dr. Albert Lyons, was really the first self-help organization for the sufferers of IBD.

Conceptual Contributions

There are four areas in which gastroenterology at Mount Sinai has made significant contributions to conceptual advances in IBD. The first was the use of actuarial life tables for postoperative recurrence and re-operation rates in IBD. The paper by Greenstein, Sachar, Pasternack and Janowitz (66), which compared crude and cumulative rates, was among the first such uses of the life tables as a statistical method in IBD. No publication on the long-term follow-up in this field can now be accepted without the use of this method of presentation.

Second, since studies of the natural history of untreated IBD patients have not been done, and cannot be done, the use of the placebo arm of controlled trials as introduced by Meyer and Janowitz, when applied to Crohn's disease (26) and UC (27), revived interest in the placebo effect in IBD.

Third, based on Greenstein and Sachar's concept, the recognition of two clinical forms of CD, a perforating and a non-perforating one, and their indications for repeated operation as published in *Gut* (67), has attracted considerable attention and recent confirmation. This concept has proved central to current classifications of patients with Crohn's disease (68).

Fourth, workers in the division have recently questioned how effective our current drugs are in the treatment of CD (69), UC (70) and severe Crohn's and ulcerative colitis (71). The first two papers used the method of meta-analysis, and the third was an analytic review of selected clinical trials. The thrust of these papers is to point out the relatively limited effectiveness of our traditional and current drug therapies.

The Role of the Fecal Stream in Crohn's Disease

Leon Ginzburg and his colleagues, Ralph Colp and Marcy Sussman (5), noted that in patients with CD, diversion of the intestinal stream led often to such clinical improvement of the primary lesion in the cecum and/or ileum that the intended 2nd stage resecting the central lesion could be "indefinitely postponed." The important observation stimulated a long-standing interest in the division on the role of the fecal stream on the pathogenesis of localized CD.

Further evidence slowly has accumulated that surgery with anastomosis is associated with a higher risk of recurrence than ileocolostomy. Emphasized by De Dombal, Goligher and colleagues (72, 73), similar findings were also pointed out by Sachar and his colleagues at The Mount Sinai Hospital (74, 75). We have confirmed this again in a new study of end ileostomy in CD (76).

As a result of these lines of evidence, we (Janowitz, Croen, Sachar) have prepared a comprehensive historical and analytic review of all the clinical and laboratory evidence in this area (77). Many, but not all, of the accepted clinical features of CD are consistent with the contributory role for the intestinal stream concept, and fit in with recent animal studies on the role of lumi-

nal bacteria in inducing ileal and colonic inflammatory changes in some spontaneous, or transgenic, or "knock-out species."

Interaction with the Official World of IBD Activity

Gastroenterologists at The Mount Sinai Hospital have played important roles as presidents of the American Gastroenterological Association (Crohn 1935, Janowitz 1972); as the chairman of the International Organization for the Study of IBD (Sachar 1989 – 1992); and in founding the new series, the *American Journal of Digestive Diseases* (Janowitz, 1968 – 1978). Sachar launched the AGA's clinical teaching project with its first unit on IBD (78), and has contributed a number of influential and lively editorials to *Annals of Internal Medicine, Digestive Diseases and Sciences, Gastroenterology, Gut, Journal of Clinical Gastroenterology,* and *The New England Journal of Medicine.*

Monographs from the division include those of Waye on endoscopy (79), Janowitz on a clinical approach to IBD (80), and G.E. Friedman on therapeutic pharmacology in gastroenterology (81), a book by Marshak and Lindner (82), and patient information books by Present and colleagues (83, 84). The place of The Mount Sinai Hospital in the clinical world of management of IBD was advanced significantly by the endoscopic techniques used by Jerome Waye. He was the first to perform colonic endoscopy without radiographic control, and has published, lectured and edited books on gastroenterological endoscopy. Members of the original gastroenterological group in IBD played a significant role in the evolving status of the American College of Gastroenterology. The following have been among its presidents: David Dreiling, Jerome Waye, Burton Korelitz, Arthur Aufses, and Lawrence Brandt.

Appendix

The Contribution of the Division of Gastroenterology to Academia: Former Fellows and Members of the GI Division since 1958

Name	Position
J. Hugh Baron	Former President, British Society of Gastroenterology; Consultant at Hammersmith and St. Mary's Hospitals, Imperial College School of Medicine, London
Alvin Gelb	Chief of Gastroenterology Division, Beth Israel Hospital, New York
Peter Banks	Clinical Director of Gastroenterology, Brigham and Women's Hospital, Boston, MA
Fred Saibil	Head of Gastroenterology, Sunny Brook Health Science Center, Toronto
Lawrence Brandt	Chief of Gastroenterology, Montefiore Medical Center, The Bronx
Jane Geders	Chief of Gastroenterology and Hepatology, Methodist Hospital, Brooklyn
Mark Korsten	Gastroenterology Fellowship Program Director and Associate Chief of Medicine, Bronx VA Medical Center
Vivek Gumaste	Chief of Gastroenterology, The Mount Sinai Service of the City Hospital Center at Elmhurst, Queens

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