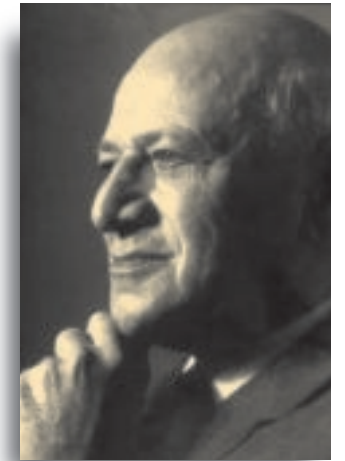
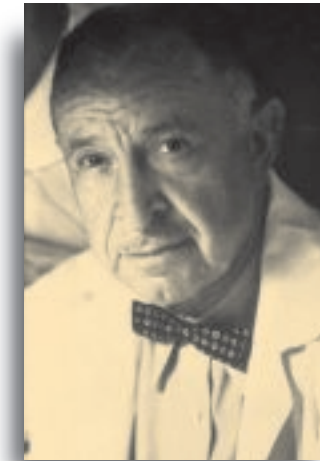




MOUNT SINAI
SCHOOL OF
MEDICINE

Mount Sinai Digest



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MOUNT SINAI
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Mount Sinai Digest

**Update from the Dr. Henry D. Janowitz
Division of Gastroenterology
Mount Sinai Medical Center**

The Mount Sinai Hospital has been at the forefront of research and treatment in Crohn's disease and ulcerative colitis before, during, and after the era of its famous trio, Burrill B. Crohn, Leon Ginzburg, and Gordon D. Oppenheimer. In this premier issue of the Mount Sinai Digest we commemorate the 75th anniversary of the seminal publication describing Crohn's disease by looking at our past, present and future contributions to the understanding and treatment of these diseases.

David B. Sachar and Daniel H. Present review Mount Sinai's history of innovation in inflammatory bowel diseases (IBD). Tom Ullman outlines the cutting edge clinical work now being done at Mount Sinai Medical Center. Finally, Maria T. Abreu looks toward the future and predicts what the next 75 years of scientific innovation might bring to our understanding of IBD.

*James F. Marion, M.D.
Editor*

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Inflammatory Bowel Disease at the Mount Sinai Hospital *The First 75 Years*

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From the Dr. Henry D. Janowitz Division of Gastroenterology, Mount Sinai School of Medicine



**Left to right: Dr. Gordon D. Oppenheimer,
Dr. Burrill B. Crohn and Dr. Leon Ginzburg**

In the years since 1932, "Crohn's disease" has become the most frequently used medical eponym in the world. Yet Mount Sinai's role in recognizing and studying this disorder extends back even earlier in the century.

Credit for one of the earliest "modern" descriptions of what we now call Crohn's disease goes to a Scottish surgeon, Kennedy Dalziel (pronounced DEE-YEL), who published his observations in the British Medical Journal in 1913, when it may have escaped notice in the looming shadow of a World War. After the war, two Mount Sinai physicians, Eli Moschowitz and Abraham Wilensky, were also reporting cases as early as 1923 and 1927, suggesting that most instances of "non-specific granulomata of the intestines" were in fact a distinct entity different from tuberculosis.

Widespread recognition of non-tuberculous granulomatous enteritis, however, was delayed until two presentations from Mount Sinai in 1932. At a meeting of the American Gastro-Enterological Association in Atlantic City on May 3, Leon Ginzburg read, on behalf of himself and Gordon

D. Oppenheimer, a pathological description of (among others) 14 cases of "localized hypertrophic ulcerative stenosis of the terminal ileum." In a parallel presentation just ten days later in New Orleans, Burrill Crohn read, on behalf of himself and Leon Ginzburg, a clinical description of 15 cases, all but one being the same that Ginzburg had presented.

Disputes over primary credit notwithstanding, over the subsequent decades both Crohn and Ginzburg, contributed mightily to the literature on this disease and, in the words of Ginzburg himself, "put regional enteritis on the map."

In 1962, Mount Sinai doctors once again were the first in America to pick up a lead from Great Britain when, following a report two years earlier by Lockhart-Mummery and Morson, they definitively established that "regional enteritis" could similarly affect the colon. In this instance, it was two radiologists, Richard Marshak and Bernard Wolf, who blazed the trail, soon joined by a GI Fellow, Arthur Lindner (later Chief of GI at New York University), and Henry Janowitz, by then already Chief of GI at Mount Sinai.

Meanwhile, in the three decades between 1932 and 1962, Mount Sinai was laying a firm foundation for the world's knowledge of IBD. In keeping with Mount Sinai's ongoing tradition of interdisciplinary collaborations, these contributions came from interactions among gastroenterologists, surgeons, radiologists, and pathologists. The results of resection and bypass were documented; toxic megacolon was described; colon cancer in ulcerative colitis was reported (by Crohn in 1925!) as was small bowel cancer in regional ileitis (by Ginzburg et al. in 1956!); and Crohn, Yarnis, and Korelitz published a pioneering study of ulcerative colitis and pregnancy.

Productivity regarding IBD accelerated at Mount Sinai for yet another 30 years from 1962-1992. Gastroenterologists and surgeons cooperated in an outpouring of observations delineating the

natural history and complications of ulcerative colitis and Crohn's disease, ranging from the classical extra-intestinal manifestations and measures of activity to groundbreaking insights into the features and risk factors of cancer in both ulcerative colitis and Crohn's disease.

Mount Sinai also led the way to early therapeutic breakthroughs like the first prospective placebo-controlled dose-ranging study of a non-sulfonamide aminosalicylate to the revolutionary and ultimately triumphant introduction of 6-mercaptopurine treatment by Korelitz and Present. Likewise, surgical therapy in a department headed by Arthur H. Aufses, Jr., himself an international authority in IBD, was advanced by Irwin Geleert's early introduction into the U.S. of the continent ileostomy and the ileal pouch and by Adrian Greenstein's early application of stricturoplasty.

Also among the publications from Mount Sinai during this period were four of what Dr. Janowitz has called "conceptual advances": the application by Greenstein and Sachar of "life-table" methods for analyzing the postoperative course of Crohn's disease; their recognition of distinct "behavioral" patterns of Crohn's disease, which has formed the basis of all subsequent efforts at clinical "phenotyping"; the analysis by Meyers and Janowitz of treatment effects by meta-analysis and by particular attention to the "placebo effect"; and a focus of attention on the role of the "fecal stream" in Crohn's disease.

These fertile decades at Mount Sinai also saw the advent of patient-oriented activities in IBD: the first

formal study of "quality of life"; the establishment by Albert Lyons of the first self-help group for ileostomy patients; and the founding by the Rosenthals, the Modells, and Dr. Janowitz of the National Foundation for Ileitis and Colitis (NFIC), now known as the Crohn's & Colitis Foundation of America (CCFA).

Finally, as we survey the past 15 years of clinical and laboratory research on IBD, we find Mount Sinai still at the forefront with studies spearheaded by Lichtiger and Present that introduced cyclosporine as a critical treatment option; multi-center clinical trials including or led by Mount Sinai that firmly established infliximab as a therapy that has by now been applied to over a quarter of a million patients; and basic laboratory investigations under the leadership of Lloyd Mayer, delineating the role of cellular immune mechanisms in the pathogenesis of IBD.

Bibliographical Note

All the pre-2000 studies and publications cited in this brief summary article are reviewed in more detail in the following historical surveys:

Baron JH, Janowitz HD (eds). Gastroenterology and Hepatology at The Mount Sinai Hospital (Theme Issue, Part II). Mt Sinai J Med 2000; 67:174-240.

Sachar DB. Planting seeds of knowledge about inflammatory bowel disease. Mt Sinai J Med 2001;68:79-87.



The founding of what is now the CCFA. From left to right: Oppenheimer, Crohn, Mr. Irwin Rosenthal, Dr. Henry D. Janowitz and Ginzburg.

The Cutting Edge: Current State of the Art Treatments for IBD at Mount Sinai

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As with all chronic illnesses, the goals of therapy in IBD are to induce a remission, maintain a remission, improve patients' quality of life, and minimize the likelihood of unwanted effects of treatment. Mount Sinai remains at the cutting edge in the development of IBD therapies.

Treatment of Crohn's Disease

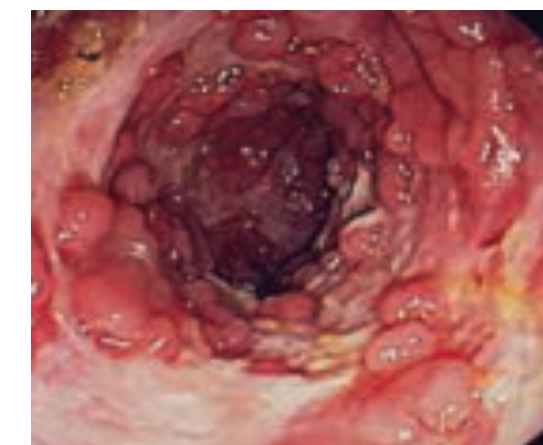
Crohn's disease can present in several ways. In some patients Crohn's disease may be purely inflammatory in nature, or, may penetrate through the serosal surface of the intestinal tract with resultant fistulae formation. In other patients, fibrostenosis or collagenous scar formation can produce obstruction. Therapy for Crohn's disease should be tailored to the type, severity and location.

While the data supporting their clinical utility are sparse, most Mount Sinai IBD-ologists use mesalamine-based agents (sulfasalazine, mesalamine, balsalazide) or antibiotics directed against gut flora in the treatment of mild, active Crohn's disease. The shortage of supporting literature for these agents for either induction or maintenance of remission is matched by their ease of use and excellent safety profile, particularly in patients with colonic disease or those with small intestinal bacterial overgrowth as a function of luminal narrowing from strictures or active inflammation. Well-designed trials are under way at Mount Sinai to address this gap in the literature.

Corticosteroids are sometimes used as second-line agents for the induction of remission, but owing to

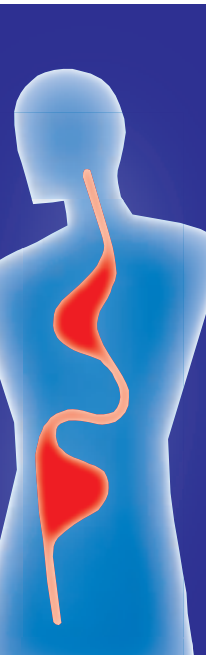
their myriad adverse effects in both the short and long-term, minimization of their use remains a priority at our institution. Ileal release budesonide, a corticosteroid four-fifths of which is converted into non-corticosteroid metabolites in first pass through the liver, may be considered a first line agent for ileal disease in the induction of remission, but its role as a maintenance medication is unclear. There is no role for prednisone as a maintenance drug, and its use to induce a remission in active disease is waning. A strategy for a different maintenance agent is an absolute requirement whenever corticosteroids are considered for induction, and we encourage all of our colleagues to consider other agents for the induction of remission when antibiotics or mesalamine prove insufficient.

The purine analogs 6-mercaptopurine and azathioprine have an excellent track record as steroid-sparing maintenance treatments for Crohn's disease, but due to their slow onset of action (8-12 weeks), have only a limited role in the induction of remission. Present and colleagues at Mount Sinai demonstrated their steroid-sparing effect more than two decades ago. Side effects limit these agents in approximately 15% of patients, with acute intolerance (fever and arthralgias or pancreatitis



Crohn's disease of the distal ileum can produce deep ulceration and nodularity known as "cobblestoning".

most commonly), leukopenia, other cytopenias, liver chemistry abnormalities, and possible infectious and neoplastic risks possible. Despite these concerns, these medicines are almost certainly underutilized in the community in the face





of over-utilization of corticosteroids. They represent the mainstay of maintenance therapy here at Mount Sinai. Methotrexate, an anti-metabolite, has also been demonstrated to be useful as a steroid-sparing agent in the maintenance of Crohn's remission. It, too, has a less than ideal safety profile, but when compared to the horrific adverse events associated with corticosteroids, benefits outweigh risks in steroid-dependent patients or in patients unable to be maintained with first line agents. We often turn to methotrexate in patients who are intolerant to 6-MP.

Anti-TNF-alpha therapy with infliximab (Remicade), adalimumab (Humira), and certolizumab pegol (Cimzia) constitute an additional alternative to corticosteroids and the purine analog immunomodulators. These agents have been demonstrated to be useful in the induction of remission, maintenance of remission, fistula closure and in steroid-sparing. Their role in closing fistula is matched only by cyclosporine, a calcineurin inhibitor, which was demonstrated in a Mount Sinai study. As monoclonal antibodies, their principle side effects are immunologic in nature with acute and delayed infusion reactions (that is not IgE mediated—also a Mount Sinai discovery) and loss of response due to antibody formation the most common manifestations. An increase risk for infections (particularly reactivation of tuberculosis), lymphoproliferative disorders (including rare cases of hepatosplenic T-cell lymphomas) and multiple sclerosis-like neurologic events are other potential but uncommon side effects. Without precise knowledge of when to stop these medications after their initiation and with the long-term adverse effects poorly understood due to their relatively recent entry into practice, controversy abounds as to when to start therapy with anti-TNF antibodies. When possible, treatment with purine analogs or methotrexate should be considered prior to committing patients to anti-TNF's. (The controversy of top-down, early anti-TNF therapy, versus bottom-up, with corticosteroids first and are somewhat convincing in favor of infliximab, is not applicable in our hands owing to our aversion to corticosteroids). A more relevant controversy is whether infliximab or adalimumab can be withdrawn after co-initiation with purine analogs. We have initiated a trial to answer that question. We typically increase its dose or frequency when response to one of the anti-TNF's wanes. If this proves unhelpful, a change in anti-TNF agent may be helpful if antibodies to the drug have formed. Measuring trough levels of infliximab are helpful in determining whether antibodies have formed (low levels) or if the disease is no longer anti-TNF responsive.

A number of other potential therapies wait on the horizon, many of which have been investigated at Mount Sinai. Visilizumab (Nuvion), an antibody against CD-3 cells (lymphocytes) has shown promise. Other antibodies against pro-inflammatory cytokines are remain intriguing possibilities as well, including antibodies to IL-12 (CNT-01275) or IL-12/23 p40 (ABT1274) (a key product of antigen presenting cells in the mucosal immune system), interferon g (fontolizumab), and IL-6 (atlizumab) among others. Therapy directed against T-cell activation, such as abatacept (Orencia) constitutes another avenue under investigation at Mount Sinai. Natalizumab (Tysabri) is an antibody therapy that targets adhesion molecules responsible for the recruitment of white blood cells to areas of active inflammation, and has been quite successful in clinical trials, but enthusiasm has been tempered by rare cases of progressive multifocal encephalopathy. Leukocytapheresis, stem cell therapy, and therapies that enhance innate immunity (GM-CSF) are other strategies not yet in routine practice that are or have been under investigation. There are always a number of active clinical trials at Mount Sinai investigating novel treatments.

Finally, although surgery is often considered a poor outcome in clinical trials, a well-timed and limited resection or stricture-plasty represent very effective therapy in the hands of a well-trained IBD surgeon, and we often recommend such surgery in patients with limited disease or disease that fails to respond to medical therapy. Secondary prophylaxis after surgery remains controversial, but use of antibiotics and/or purine analogs in complicated patients with rapid progression to surgery, a history of multiple surgeries, or complex fistulous disease represent the current state of the art and what most of us prescribe for our patients following surgery.

Treatment of Ulcerative Colitis

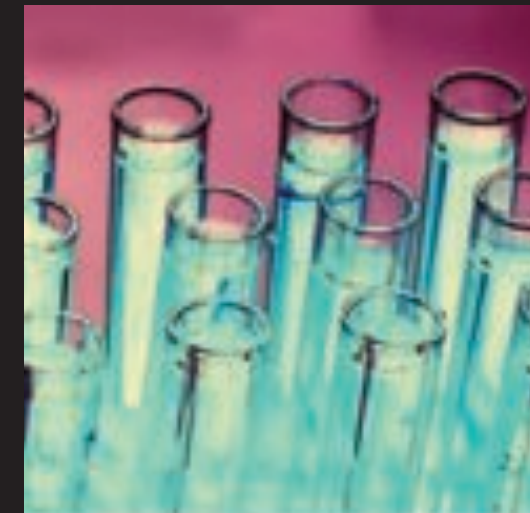
First line therapy for the treatment of ulcerative colitis is mesalamine-based therapy. As opposed to its use in Crohn's disease, the data supporting mesalamine-based therapy in UC is outstanding. The addition of rectal mesalamine to oral mesalamine increases the rate of remission and shortens the time to remission, and should always be considered. Data supporting its role in maintenance is also outstanding.

When mesalamine therapy fails in a patient in the midst of a flare, the principle option is corticosteroid-based therapy, again with a planned exit strategy and the addition of a drug for maintenance, usually 6MP or azathioprine. When and whether to start infliximab for moderate to severely affected patients is unknown. Other anti-TNF agents may be useful in UC, though publications directly supporting this are few. As with Crohn's disease, a number of agents are under investigation at Mount Sinai.

For the patient needing hospitalization, severely active UC, intravenous corticosteroids and intravenous cyclosporine are the mainstays of therapy at Mount Sinai. The role of anti-TNF therapy in this group of patients is uncertain. In these patients (as in all active IBD patients), consideration for infection or superinfection with *Clostridium difficile*, CMV, and other microbes should be considered and excluded. Surgery with either restorative proctocolectomy or total proctocolectomy with ileostomy is usually reserved for patients with medically refractory disease, patients with cancer or dysplasia, or patients with colitis-related complications (such as hemorrhage, infection, or hypercoagulability, for example).

The Next 75 Years: Future Innovations

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The future is bright for both patients and clinicians dealing with inflammatory bowel disease. Many scientific advances will be translated to the bedside in the coming years. The area that has been the most fruitful recently has been the area of genetic research in inflammatory bowel disease. This has been facilitated by advances in technology that allow the simultaneous assessment of a million different genetic variants in a given individual simultaneously. In the past, each of these genetic changes needed to be evaluated one by one and so for the most part, most genetic research in inflammatory bowel disease focused on looking at small differences (one or two genes at a time) between individuals who had inflammatory bowel disease and those that did not. Currently however, the standard has been to use what is called genomewide scanning to look at these changes simultaneously using chip-based approaches.

There have already been several important discoveries made using these approaches. The first has been that investigators in more than one study have found that genetic variants, otherwise known as polymorphisms, in the interleukine-23 (IL-23) receptor are involved in Crohn's disease. The reason this is interesting is because IL-23 is in a place in the immunological cascade that would predict that changes in the cytokine may result in inappropriate amounts of inflammation. Although it

has not happened yet, it is likely to be the case that biotech companies will be looking at IL-23 and some of the cytokines downstream of IL-23 to treat patients that have inflammatory bowel disease, in particular, Crohn's disease. The other interesting thing about the genetic research in inflammatory bowel disease is the fact that the recurrent theme of a lot of this research is that polymorphisms in genes that are involved with the innate immune response keep appearing on the list of genes associated with IBD.

We have focused a lot of our attention in the last several years on the adaptive immune system. The adaptive immune system is the part of the immune system composed of T-cells and B-cells that generates responses to very specific proteins or bacteria. By contrast, the innate immune system is there to provide a very rapid response to pathogens. Therefore what makes this interesting is that changes in the ability to have a rapid response to bacteria may be more important in inflammatory bowel disease than these more specific immune responses in the adaptive immune system. On the basic science side, again, the innate immune system appears to feature prominently in inflammatory bowel disease animal models. These findings will likely result in big changes in the way we currently treat inflammatory bowel disease. In fact, most of the therapies that we use for inflammatory bowel disease actually suppress innate immunity.

The most powerful way to suppress innate immunity is probably to use corticosteroids. Obviously that seems to be a misguided approach in the long-term for patients with ulcerative colitis and Crohn's disease. Finally, the future of inflammatory bowel disease is going to rest on a more calculated approach to using medicines for specific patient groups. For instance, there may be people who have a great response to anti-TNF therapy. There is a good third of patients who do not have a very good response to anti-TNF therapy. In the future we will be using genetic tests as well as serological tests to try to fine-tune who will benefit best from these therapies and match the therapy better with individual patients. This offers a promise of having better outcomes and in particular avoiding adverse events from therapies that are less likely to be effective.