Historical Perspectives: Malignancy in Crohn's Disease and Ulcerative Colitis

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Abstract

While both Crohn' disease (CD) and ulcerative colitis (UC) are known to predispose patients to certain intestinal malignancies, the exact mechanism of carcinogenesis remains unknown and optimal screening guidelines have not been established. This article will explore the history of our understanding of intestinal malignancy in inflammatory bowel disease (IBD). To contextualize the medical community's difficulty in linking each condition to cancer, the first section will review the discovery of CD and UC. Next, we discuss early attempts to define IBD's relationship with small bowel adenocarcinoma and colorectal cancer. The article concludes with a review of each disease's surgical history and the ways in which certain procedures produced poor oncologic outcomes.

Keywords
- historical review
- Crohn's disease
- ulcerative colitis
- cancer
- inflammatory bowel disease

Inflammatory bowel disease (IBD), which consists of Crohn's disease (CD) and ulcerative colitis (UC), affects 1.6 million persons in the United States.[1] The exact pathogenesis of these conditions remains unknown, but involves complex interactions between the body's immune system, intestinal flora, environmental stimuli, and individual genetics. While IBD patients are widely recognized as high risk for certain intestinal malignancies, our understanding of this association has not always been clear.

This study will review the history of intestinal cancer in IBD. For the purpose of contextualizing the medical community's struggle to understand IBD's connection to malignancy, we will outline each condition's discovery. Next, we will discuss early attempts to define the risk, etiology, and prognosis for IBD patients with small bowel adenocarcinoma (SBA) and colorectal cancer (CRC). Finally, we will review the surgical history of each disease and the ways in which certain procedures have resulted in poor oncologic outcomes.

Crohn's Disease

History of Crohn's Disease

In their landmark 1932 paper, Crohn et al described 14 cases of an inflammatory disease affecting the terminal ileum, which they named "regional ileitis."[2] Leon Ginzburg and Gordon Oppenheimer were young researchers working in the surgical laboratory at the Mount Sinai Hospital studying granulomatous diseases of the intestine, when they, together with Burrill Crohn, the Chief of Gastroenterology, recognized that the inflammatory process in these cases was distinct from that seen in tuberculosis or sarcoidosis (►**Fig. 1**). Over the years, the disease was called "regional enteritis," "granulomatous enteritis," and "transmural colitis," until finally inheriting the eponym of Crohn's disease.[3]

In retrospect, the medical literature contains multiple published reports of Crohn's-like pathology as early as the 18th century. Morgagni (1769),[4] Coombe and Saunders (1813),[5] and Abercrombie (1828)[6] described sporadic cases of mostly young patients with histories of chronic, fluctuating abdominal pain who were found on autopsy to have severe ileal inflammation, mucosal ulceration, and adjacent lymphadenopathy. Although these lesions were mostly attributed to tuberculosis, which was prevalent at the time, Dalziel reported a case series of tuberculosis-negative patients with chronic intestinal inflammation in 1913.[7] He performed several successful bowel resections and described the appearance of one patient's diseased bowel as similar in "the consistence and smoothness of an eel in a state of rigor mortis."[7]

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Fig. 1 Photo of Dr. Leon Ginzburg (Left) and Dr. Burrill B. Crohn (right) at the 50th Anniversary IBD symposium at Mount Sinai in May 1982. (Reproduced with permission from the Arthur H. Aufses, Jr. MD Archives, Icahn School of Medicine at Mount Sinai/Mount Sinai Health System, New York, NY; and Bornstein and Steinhagen.[14])

After Crohn et al recognized "regional ileitis" as a distinct disease entity, there remained significant debate as to the etiology and extent of the disease process. Clinicians believed that the condition consisted of four stages. These included an acute phase mimicking acute appendicitis, an ulcerative stage with colicky abdominal pain, an obstructive stage caused by stenotic lesions, and a fistula-forming stage.[8] Explanations of the disease's etiology included theories that involved bacterial infection, viral illness, tuberculosis, foreign body reaction, impaired blood supply, and even possible psychosomatic origin.[8–10]

Another equally important debate focused on the extent of the disease itself. Almost as soon as Crohn et al published their original paper on "terminal ileitis," multiple physicians argued that the disease should be called "regional enteritis," due to numerous reports of granulomatous inflammation affecting the proximal small bowel.[3] In subsequent years, the disease was found throughout the alimentary tract, including duodenum,[11] stomach,[12] and esophagus.[13]

While clinicians readily adopted the term "jejuno-ileitis" to characterize disease affecting the proximal small bowel segments, there remained great hesitation to accept that CD could involve the colon.[14] This was despite evidence appearing as early as Coombe and Saunders' 1813 report, which described a patient with three colonic skip lesions in addition to ileal inflammation.[5] Four years after the 1932 article, Crohn and Rosenak reported nine patients with terminal ileitis and segmental colonic inflammation (►**Fig. 2**).[15] However, the authors believed that the colonic involvement was coincidental and perhaps a form of UC. In 1952, Wells identified a process that he termed "segmental colitis," which "closely resembles the lesions of the colon seen in terminal ileitis…[and] is characterized by patchy ulceration of the mucosa and tendency to spread by skips."[16] While Wells argued that this pathology was a colonic form of CD, his opinion was not widely accepted until Lockhart-Mummery and Morson's 1960 description of 25 colonic CD cases.[17] In the 1970s, the advent of the Crosby capsule enabled researchers to definitively prove by biopsy that Crohn's patients had histological abnormalities throughout the entire alimentary tract, even in areas without active inflammation.[3]

Recognizing the Association between Crohn's Disease and Malignancy

The history of CD reveals that its etiology, progression, and extent beyond the distal ileum remained hotly contested

Fig. 2 Dr. Burrill Crohn at light box, 1958. (Reproduced with permission from the Arthur H. Aufses, Jr. MD Archives, Icahn School of Medicine at Mount Sinai/Mount Sinai Health System, New York, NY.)

topics for several decades following the initial description. For this reason, the disease's association with intestinal carcinoma went largely unrecognized until the 1970s. Warren and Sommers reported the first case of a Crohn's patient with ascending colon cancer in 1948,[18] while Ginzburg et al published the first case of SBA arising from an inflamed jejunal segment in 1956.[19] With so few cases reported in the literature, these malignancies were considered coincidental, and it took decades to better define the association between CD and cancer.

Small Bowel Adenocarcinoma

Several sporadic case reports of small bowel cancer followed Ginzburg's initial publication in 1956, raising suspicions that CD may predispose patients to SBA. However, with less than 100 cases published in the literature by the 21st century, any attempt to define this relationship was inherently limited by small sample size. Using imperfect methods, researchers estimated that Crohn's patients had anywhere from a 6 to 320 times increase in relative risk of developing SBA.[20–23]

Early retrospective studies noted that in contrast to de novo cases, SBA in CD tended to occur at the terminal ileum, develop from areas of active enteritis, and occurred at a younger age.[21,24–28] While SBA in the general population was already difficult to diagnose and was associated with poor oncologic outcomes, Crohn's patients appeared to have an even worse prognosis. In the 1980s, CD-associated SBA had a 9% 2-year disease-free survival rate compared with 15 to 23% in sporadic cases.[28] Researchers argued that a delay in diagnosis explained these poor outcomes, highlighting that the most common presenting symptoms, such as abdominal pain, obstruction, and diarrhea, mimicked a Crohn's exacerbation.[20,29] As such, patients often experienced months or even years of symptoms before diagnosis. The vast majority of cancers were discovered unexpectedly in the operating room, by which point over 30% of patients had metastatic disease.[30,31] Despite improvements in imaging modalities, SBA remains difficult to diagnose and there are no recommended screening guidelines for Crohn's patients.[31,32]

Colorectal Cancer

The medical community did not believe that CD could predispose patients to CRC until the 1970s. Unlike UC, where researchers had established that malignancy arose from dysplastic epithelial changes, the few published cases of CD-related colon cancer did not appear to consistently develop from areas of active disease.[33] Thus, experts at the time concluded that the "management of Crohn's colitis should not be influenced by the probability of malignant change."[34]

General opinion began to shift several years later, after Weedon et al published a retrospective review of 449 Crohn's patients treated at the Mayo Clinic. Eight patients developed CRC at a median age of 33. Compared with population data available at the time, these patients developed cancer at a rate 20 times greater than expected.[35] Other attempts to better quantify the risk of colon cancer in CD relative to UC yielded variable results. While some studies showed that Crohn's patients had a much lower risk of malignancy, others found that the incidence of CRC was almost identical at 7 and 8%.[21,36,37] Patients with early-onset disease, extensive colonic involvement, and those who developed colonic strictures had increased risk of malignancy.[36,38,39] Given this uncertainty, it took several decades for Crohn's patients to be included in CRC surveillance screening guidelines.[40]

Malignancy and Surgical Procedures for Crohn's Disease

Few treatment options existed for patients at the time of the initial description. Medical therapy alone was often ineffective, and consisted of bed rest, high-protein diets, hydration, alpine light, and "X-ray therapy."[8] While surgery was regarded as offering a potential cure, procedures were generally reserved for severe cases as the risks of surgery were substantial. Even before CD had been defined as its own pathologic entity, surgical management of "regional enteritis" consisted of a radical resection, including excision of the diseased segment, mesentery, and all associated inflamed lymph nodes.[7,8] Surgeons believed that it was important to remove all active disease, and general practice was to transect the ileum 2 feet proximal to the edge of visible inflammation.[41] Mortality rates from this procedure in the 1930s were high, with reports ranging from 13 to 22.8%.[8,41]

Bypass

In 1942, Colp et al published a series of 40 Crohn's patients at Mount Sinai treated with an exclusion bypass procedure. Initially intended as the first portion of a multistage resection, the diseased ileum was divided proximally by several feet, the divided distal end inverted, and the proximal segment anastomosed to the transverse colon.[42] In contrast to the high mortality rates associated with resection, the Mount Sinai group reported no deaths and symptomatic improvement in 90% of patients.[42]

While this approach gained popularity and was widely used throughout the 1940s and 1950s, it began falling out of favor for several reasons. Primarily, mortality rates following resection dropped dramatically with improvements in anesthesia and perioperative care.[3,43] Second, clinicians caring for these patients began to recognize that the disease frequently recurred, even if all macroscopically visible inflammation had been resected.[3] Multiple studies comparing operative techniques demonstrated that exclusion bypass, which left diseased bowel in situ, had significantly higher recurrence rates than resection.[44,45] Finally, reports began to appear of SBA arising in excluded segments. By 1975, Lightdale et al reported that 37.5% of all published SBA cases occurred in excluded loops.[46] Several years later, Greenstein et al published a detailed report of seven cases of cancer in excluded segments. All patients in this series had abysmal outcomes, with metastatic disease diagnosed at time of laparotomy and a 100% 2-year mortality rate.[47] Not only was it unsafe to leave severely diseased bowel behind in an operation, but also these patients likely experienced an even greater delay in diagnosis as a result of cancer developing in the excluded segment.[29,31,47]

Strictureplasty

As disease recurrence became an accepted aspect of CD, physicians encountered a growing number of patients who required multiple operations. Given the practice of taking excessively wide resection margins, there was real risk that multiple procedures could lead to short bowel syndrome. These concerns led Lee and Papaioannou to attempt strictureplasties on Crohn's patients in 1982.[48] Katariya, an Indian surgeon, first used a strictureplasty technique in 1977 to treat patients with tubercular strictures.[49] Lee and Papaioannou's work demonstrated that strictureplasty was an effective way to preserve bowel length and that suturing through macroscopically diseased intestine did not result in high postoperative leak rates.[48] Critics of this technique raised similar concerns to those regarding bypassed segments, primarily that diseased bowel was being left in situ and could predispose patients to SBA.[50] However, these fears appeared to be overstated as malignancy rarely occurred at the site of a Crohn's stricture.[39,44] While some surgeons advocated for routine biopsy of strictured segments before performing a strictureplasty, others argued that this should only be done in the setting of visible mucosal abnormalities.[20,29,44]

In 2001, Jaskowiak and Michelassi reported a case of a 47-year-old man with a long history of CD who presented with intermittent obstruction and was found to have adenocarcinoma at his strictureplasty site.[51] Over the next few years, similar reports were published by Partridge et al[52] and Menon et al.[53] To date, the incidence of SBA arising from a Crohn's stricture is estimated to be only 0.3%, and there are only a handful of reported cases associated with a strictureplasty site.[54] Given the rare incidence, society guidelines do not recommend routine biopsy during strictureplasty.[55]

Ulcerative Colitis

History of Ulcerative Colitis

UC may have been described as early as the Greek classical period, when Hippocrates of Kos detailed a particular type of diarrhea containing blood and mucous-streaked stool.[3,56,57] However, it was not until the 19th century that Sir Samuel Wilks and Walter Moxon were credited with recognizing UC as a distinct pathologic entity from other forms of diarrhea.[58] Multiple case reports followed, and by the late 1800s, the term "ulcerative colitis" had become ubiquitous in the medical literature.

Clinicians observed that patients tended to present in early adulthood, had frequent blood-tinged bowel movements resulting in anemia, and were susceptible to disease relapse.[59,60] In 1909, Mummery described the appearance of

mucosal ulcerations on sigmoidoscopy and noted the new tool's utility in aiding diagnosis.[61] Autopsies revealed that the disease always involved the rectum, but in severe cases, could uniformly affect the entire colon.[60] On pathologic examination, specimens could range from "complete destruction of the mucous membrane over large areas, to merely a few discrete ulcers in the lower part of the bowel."[59] Helmholz first described UC in children in 1923,[62] and Spriggs identified a familial predisposition in 1934.[63] Similar to CD, the etiology of UC remained elusive, with physicians advocating for a range of causes, including bacterial infection, exposure to a tropical climate, and psychological disturbances.[59,60,64]

For patients diagnosed with UC in the early 1900s, outcomes remained dismal. With medical treatments limited to dietary modifications and rectal irrigations, many patients progressed to severe fulminant disease and occasionally colonic perforation.[3,59,61] Estimates from London area hospitals in 1907 suggested a mortality rate between 44 and 78% for all patients admitted with UC.[59,61]

Ulcerative Colitis and Colorectal Cancer

The first reports of UC-associated CRC were published in the 1920s, and soon thereafter there was widespread acceptance that UC is a premalignant condition.[65–67] Initial estimates put the cumulative 10-year risk of developing CRC as high as 25 to 30%.[68–70] Subsequent population-based studies demonstrated a lower, but still considerable, risk of 2, 8, and 15% after 10, 20, and 30 years of disease.[71] In addition to developing cancer at a younger age, UC patients with pancolitis, primary sclerosing cholangitis, and more than 10 years of symptoms appeared to be at particularly high risk of cancer.[68,72–74]

The exact mechanism by which UC patients develop CRC remains unknown. However, carcinogenesis likely arises from complex interactions between chronic inflammatory disturbances and the gut microbiome.[75] Despite advances in scientific knowledge, it remains unknown whether stringent endoscopic surveillance programs, more sophisticated endoscopy techniques, or improved disease control with biologics reduces the incidence of malignancy.[22,76]

Differences in Ulcerative Colitis and Sporadic Colorectal Cancer

As early as 1927, Yeoman and Bargen suggested that carcinoma in UC may develop from a pathway involving inflammatory-induced mucosal changes and adenoma formation.[60,65] While physicians knew that sporadic CRC often formed in the setting of premalignant adenomatous polyps, UC-related cancers appeared to follow a different pathway. Since first described by Habershon in 1862, UC had been linked to the formation of pseudo-polyps.[77] While many scholars thought that these pseudo-polyps were responsible for malignant degeneration, pathologic examination demonstrated that the majority of UC-related CRC developed in the absence of these lesions.[72,78–80] Counsell and Dukes noted that UC carcinomas could present as an inflammatory stricture or could appear macroscopically to have "no visible neoplastic lesion on the [mucosal] surface."[72] In patients with extensive colitis, the entire colon appeared to be at risk, with synchronous cancers diagnosed in 22% of UC patients compared with 3% in the general population.[34] Our current understanding of CRC is that cancer develops out of a series of genetic mutations. While sporadic cancers acquire mutations in the *adenomatous polyposis coli* (*APC*) gene followed by mutations in *p53*, this process is reversed in IBD.[75]

Discovery of Dysplasia and a Role for Surveillance Endoscopy

Real advances in our understanding of carcinogenesis in colon cancer came with the discovery that dysplasia represented a precancerous change. Research in the 1960s proved that cervical cancer developed through a series of dysplastic changes. Morson and Pang made a significant contribution to this topic by characterizing the appearance of dysplastic changes in rectal biopsies.[81] Not only did the authors demonstrate diffuse evidence of dysplasia in UC colectomy specimens, but also they established a pilot surveillance program for UC patients consisting of annual sigmoidoscopy with rectal biopsy. Patients with dysplasia proceeded to surgery. While not every patient had invasive adenocarcinoma on pathology, Morson and Pang concluded that "recognition of precancer in a rectal biopsy is associated with a high incidence of suspected or unsuspected invasive carcinoma in the more proximal bowel."[81]

This new surveillance program offered hope that physicians could detect malignancy in UC patients before cancer progressed to a late stage. Surgeons readily acknowledged that existing methods, such as barium enema or proctoscopy alone, were often ineffective at detecting early cancers.[82] In the 1960s, close to 20% of patients were inoperable at presentation, and 5-year survival for UC-related CRC was 18.6%.[34,82] Surveillance programs became increasingly common throughout the next decade, but clinicians were unable to monitor the entire colon until the advent of colonoscopy in the 1970s.[40] Despite these improvements, many surgeons cast doubt on the reliability of endoscopic screening to detect cancer and instead advocated for prophylactic total proctocolectomy after 10 years of symptoms.[74] In the 1980s, Lennard-Jones et al published a 15-year follow-up of over 300 UC patients in a surveillance program. While dysplasia on biopsy did not always correlate with malignancy, the authors noted that 87.5% of cancers were diagnosed at an early stage with excellent 2-year survival outcomes.[83] Although imperfect, endoscopic surveillance remains the gold standard for monitoring cancer risk in UC patients. Ongoing debates regarding the optimal surveillance interval and the necessity of resection once dysplasia has been detected lie outside the scope of this study.

Malignancy and Surgical Procedures for Ulcerative Colitis

Mayo-Robson performed the first surgery for UC in 1893, where he formed a temporary colostomy to allow for bowel rest in a patient with severe colitis.[3] In 1900, Lilienthal at the Mount Sinai Hospital reported the first successful colectomy for UC.[84] By the early 1900s, appendicostomy and valvular

cecostomy were the standard surgical approaches for UC. Both procedures created an orifice, which allowed for irrigation into the proximal colon.[57] Surgeons at the time believed that irrigations could cure the colonic inflammation, and that it was safe to allow the opening to close once a patient's symptoms improved.[56] These procedures did little to divert the fecal stream, and several prominent surgeons began advocating for an alternative approach.[57,59,64]

In 1913, Brown attempted the first ileostomy, which was fashioned flush with the skin in a midline wound.[85] In most cases, the colon was left in place, as the ileostomy diverted all fecal contents. The procedure was fraught with complications from dehydration, electrolyte disorders, skin excoriation, and stoma malfunction.[56] With a mortality rate of 30%, Corbett noted that ileostomy was considered "a drastic procedure and for this reason very few physicians or surgeons are prepared to submit their patients to it."[57,64]

Total proctocolectomy became the standard surgical treatment in the 1940s. By this time, physicians had realized that restoring continuity often led to disease reactivation and that patients with a retained colon could still develop CRC.[78,82] Several advances in the 1940s made the management of a permanent ileostomy more feasible. First, Koernig invented an adhesive rubber bag that provided patients with an apparatus to contain stoma output.[3] In addition to improved stoma care, Brooke developed the Brooke ileostomy technique, which reduced the incidence of stoma prolapse, retraction, and serositis that had plagued earlier ileostomies.[86] Total proctocolectomy was initially performed as a multistep process, but techniques eventually improved enough to allow surgery to occur in a single stage.[3,64] Given the high incidence of CRC after 10 years of disease, many surgeons advocated for prophylactic total proctocolectomy after a decade.[70,87] Others were hesitant to commit their patients, who were typically quite young, to a life-long ileostomy.[70,88] Even with the introduction of better surveillance programs, UC patients continued to develop CRC at high rates. The preventative potential of removing the entire colon was undeniable; however, it took decades of innovation to develop surgical techniques that reduced malignant potential while preserving continence.

Ileorectal Anastomosis

The ileorectal anastomosis was developed as an alternative to committing UC patients to a permanent ileostomy. Devine performed the first ileosigmoid anastomosis in 1943 as part of a three-stage operation.[89] A decade later, Aylett published a series of patients who successfully underwent a side-to-side ileorectal anastomosis with satisfactory functional outcomes.[88] Critics of this procedure raised concerns that leaving the rectum in place put patients at risk of developing proctitis or rectal cancer in the future.[87] Aylett defended the operation by arguing that cancer "is unlikely to exist in the residua of the large bowels which have been retained, in view of the great improvement in the patients' general condition and the subsidence of the inflammatory changes."[88] Unfortunately, long-term results proved otherwise, with an estimated 6% of patients developing rectal cancer at 20 years.[70,87,90] Recognizing this risk, surgeons began endoscopic surveillance of the rectum, but the need to provide patients with better oncologic outcomes remained obvious.

Ileal Pouch-Anal Anastomosis

While it was broadly accepted that UC patients with a retained rectum were at risk of malignancy, attempts to develop an ileoanal anastomosis technique were hindered by poor operative and functional outcomes. Nissen performed the first ileoanal anastomosis in 1932 on a child with adenomatosis coli.[56] The procedure was not seriously attempted again, until Ravitch and Sabiston performed a series of experiments in dogs.[91] However, the operation remained plagued by significant incontinence, debilitating bowel frequency, and propensity for leaks. In 1978, Parks performed the first modern version of what we typically consider an ileal pouch-anal anastomosis (IPAA) today. Inspired by the use of the Koch pouch in continent ileostomies, Parks fashioned an S-shaped ileal reservoir and performed a mucosectomy by stripping the residual rectal mucosa.[92] Approximately half of his patients were unable to spontaneously evacuate the pouch, and Utsunomiya later revised the procedure to the J pouch formation that we are familiar with today.[93] Others developed a stapled anastomosis in place of a mucosectomy with handsewn anastomosis, claiming that this technique better preserved anal sphincter function.[94,95]

Original proponents of the IPAA believed that the procedure removed all residual tissue affected by UC and therefore brought the patient's risk of developing CRC to zero. However, long-term follow-up of IPAA patients has shown that rectal cancer can still infrequently develop at the anal transition zone.[96,97] To date, no studies have demonstrated a difference in oncologic risk between stapled or handsewn IPAA.[96,97] Notably, patients who have undergone mucosectomy are not immune to this risk, as they can harbor islets of rectal mucosa.[95,96] Although imperfect, IPAA offers a significant quality-of-life improvement for patients while reducing their cumulative CRC risk to 2.4% at 20 years.[96]

Conflict of Interest

R.S. received honorarium from University Hospital, Case Western Reserve University, Department of Surgery; provides expert testimony for multiple law firms.

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