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REVIEW ARTICLE

A tale of two diseases: The history of inflammatory bowel disease☆

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Abstract

'Inflammatory bowel disease' (IBD) sounds like a straightforward term — a disease of inflammation in the bowel. However, the history of IBD reveals a story of a nefariously complex set of idiopathic conditions. IBD defies definition, in part because its pathophysiology is not completely understood. For the same reason and despite substantial advances in research, IBD also defies cure. At best, IBD can be defined as a disease of disruption — disrupted physiology, microbiology, immunology and genetics. The term 'IBD' is most often used to describe two separate conditions: ulcerative colitis (UC) and Crohn's disease (CD). This paper reviews the history of IBD, considering the ever-evolving understanding of both UC and CD. Beyond its intrinsic interest, the history of IBD exemplifies a pattern that is becoming increasingly familiar in the 21st century — the story of a chronic, incurable disease that defies the best efforts to treat it.

Contents

Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine; CD, Crohn's disease; GI, gastrointestinal; IBD, inflammatory bowel disease; RCT, randomized controlled trial; TNF-α, tumor necrosis factor alpha; UC, ulcerative colitis.

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1. Ulcerative colitis

1.1. Discovery and definition (ancient times — 1909)

Ulcerative colitis (UC) is a disease of mucosal inflammation limited to the colon, often characterized by bloody diarrhea, tenesmus and abdominal pain.[1] UC was the first subtype of inflammatory bowel disease (IBD) to be characterized as a distinct entity. Thus, the early history of IBD is the history of UC. But this is not to say that UC appeared before Crohn's disease (CD) — both conditions were likely afflicting patients long before modern medicine was able to distinguish them.

The earliest descriptions of ulcerative colitis are subject to debate. There are reports by physicians of chronic diarrhea dating back to Greek antiquity.[2] Even Hippocrates (~460–370 BCE) discussed the many possible etiologies of diarrhea.[2] The prominence of inflammation of the gut was featured in several early 19th century medical schools. Both François-Joseph-Victor Broussais (1772–1838 CE) and John Brown (1810–1882) put forth theories that all diseases derived from inflammation in the GI tract.[3] This theory arose from a rise in anatomical investigation and in the use of the microscope at this time. Also, waves of cholera spread across the globe in the 19th century, drawing attention to communicable causes of diarrhea.[4]

Sir Samuel Wilks (1824–1911), in a case report written in 1859, was the first physician who used the term "ulcerative colitis" to describe a condition similar to what is understood as UC today.[5] Reports of similar cases of a severe and persistent diarrheal disease that did not appear to be of infectious origin accumulated over the latter half of the 19th century. In 1888, soon after the advent of germ theory, Sir William Hale White of London (1857–1949) published a thorough description of cases he had seen of "ulcerative colitis" that defied any other known causes, such as "growth, dysentery, tubercle, typhoid and so forth."[6] It is from this report that the term "ulcerative colitis" entered into the general medical vocabulary.

1909 was a seminal year for UC. In January, the Royal Society of Medicine in London held a symposium where over 300 cases of UC collected from London hospitals were presented and discussed.[7] The discussions reveal many meticulous observations — from risk factors ("early adult and middle age") to common presenting symptoms ("diarrhea and hemorrhage") to treatment attempts ("Numberless have been the drugs, astringents, antiseptics, and sedatives that have been administered by the mouth with little or no assured benefit").[7] In the same year, John Percy Lockhart-Mummery (1875–1957) also demonstrated that sigmoidoscopy was a safe and invaluable tool for colonic evaluation and diagnosis.[8] Then in March of the same year, the *British Medical Journal* published Herbert P. Hawkins "Address on the natural history of ulcerative colitis and its bearing on treatment."[9] This lecture, read before the Bristol Medico-Chirurgical Society explains, "nothing can be done until the natural history of the disease is understood." He illustrated the disease through cases and proposed that the "active bacterial agents" responsible for the disease be found so that they could be controlled.

1.2. New treatments and expanding interest (1910–1950)

In the decades following 1909, the medical community's understanding of UC grew in leaps and bounds. This period included Lewisohn's detailed demonstrations of familial predisposition[10]; Hewitt's association between UC and polyps[11]; and Wangensteen's recognition that it heralded colon cancer.[12] The first report of UC in children came in 1923 by Helmholz, which included children from ages 8 to 15.[13] Advances in treatment, such as ileostomy[14] and blood transfusion[15] were proposed and then validated as therapeutic measures useful for patients with UC.

Initially, surgical treatment of UC was sporadic and mostly experimental. But after 1930, surgical interventions for UC gradually became standardized. Several of these techniques were later abandoned, but a few are still in use today. Surgical therapies that were eventually discarded include: therapeutic pneumoperitoneum,[16] appendostomy[17] and vagotomy.[18] Surgical interventions that have withstood the test of time include: ileostomy[19] and subtotal or total colectomy.[20] Medical interventions also ranged from the benign to the whimsical. These included feeding raw porcine small bowel to patients (so-called 'organotherapy'),[21] and using 'ionization therapy.' The latter entailed irrigating the bowel with a zinc solution and then running an electric current through the solution.[22]

By the 1940s, other medical specialties began to take interest in UC. Warren and Sommers published the first extensive description of the pathology of UC, with

photographs and micrographs depicting vasculitis and crypt abcesses.[23] Radiologic descriptions were increasingly used to evaluate extent of disease and identify strictures.[24] At this time, psychiatry had also been reborn as a biological science.[25] Throughout the 1930s and 1940s, many reports connected UC and psychiatric conditions,[26] — one study, by Erich Wittkower (1899–1983) claimed, "the degree of difference from average individuals was so gross as to make a special control group unnecessary."[27] Wittkower's study found 28 of 40 UC patients had emotional trauma that preceded the onset of disease. Pyschotherapy was reported to have resolved some cases of UC and helped promote remission in others.[28] It is now well understood that IBD symptoms can cause significant psychological stress. Thus, current management guidelines encourage physicians to manage the psychosocial, as well as the organic, manifestations of IBD.[1,29]

1.3. UC therapy and immunology in the modern medical era (1951–present)

Following World War II, the era of randomized clinical trials (RCTs) began, ushering in the modern age of evidence-based medicine. A landmark UC study from this time was Sloan's exhaustive series of the clinical features of 2000 UC patients published in 1950.[30] Subsequent clinical trials began to establish the efficacy of pharmacologic interventions. In 1955, Truelove published the first blinded, controlled trial in UC patients in the *British Medical Journal*, demonstrating improvement and decreased mortality for patients taking corticosteroids when compared to control subjects.[31]

A major conceptual shift followed the report of Swedish physician Nanna Svartz (1890–1986), who serendipitously discovered impressive UC symptom resolution after treatment with sulfasalazine.[32] In an attempt to cure the arthritis of his King, Gustas V, Svartz had synthesized this new drug by chemically bonding sulfapyridine, a known antibiotic, with 5-aminosalicylic acid (5-ASA or mesalasine), an anti-inflammatory. When reviewing his trial data, Svartz noticed that those arthritis patients who also had UC experienced symptom relief.[33] Years later, another RCT would demonstrate that the 5-ASA component of sulfasalazine was also effective for UC,[34] thus providing another anti-inflammatory drug for treating UC with a better adverse effect profile than sulfasalazine.

In the 1960s, Bean et al. found that the immunosuppressive drug mercaptopurine (6-MP) was efficacious in patients with UC.[35,36] As one of the first designer drugs, 6-MP was initially intended for use as a chemotherapeutic agent; it had been invented through clever application of chemistry to metabolic biology. 6-MP inhibits cell proliferation by mimicking purine structure and thus acting as a wrench in the gears of DNA synthesis. Inhibition of DNA synthesis most markedly affects rapidly dividing cells, such as inflammatory cells. The discovery (by Sir James W. Black and Gertrude B. Elion) was eventually recognized with the 1988 Nobel Prize in Physiology or Medicine.[37] In the 1970s, another thiopurine-family drug, azathioprine, which is metabolized into 6-MP, was also shown to be effective for treating UC.[38] Azathioprine was compared to sulfasalazine in a randomized controlled trial in 1975, which meticulously demonstrated the similar efficacy of these drugs.[39] An unfortunate disadvantage of this particular family of drugs is the risk of complications from bone marrow suppression. In 1980, it was found that patients with polymorphisms in the enzyme thiopurine methyltransferase (TPMT) were especially at risk for such complications due to decreased drug inactivation.[40] Thus, *tpmt* gene variation is increasingly being measured in patients before starting azathioprine or 6-MP therapy.

A major evolution in medicine in the last 60 years has been the application of molecular biology and genetics to the understanding of disease. More than a thousand manuscripts have been published investigating the immunology and molecular biology of UC. This massive amount of data serves as a testament to its complexity and ever-elusive etiology. Currently, a leading theory of UC etiology postulates an autoimmune reaction following a disordered immune response to an unknown colonic bacteria.[41] Molecular techniques have revealed that the cytokine 'tumor necrosis factor alpha' (TNF-α) plays a central role in the IBD inflammatory process. Thus, anti-TNF-α monoclonal antibodies, such as infliximab and adalimumab, have been developed to inhibit the action of TNF-α. These biologic drugs are now used to treat severe and refractory UC (Fig. 1).[42]

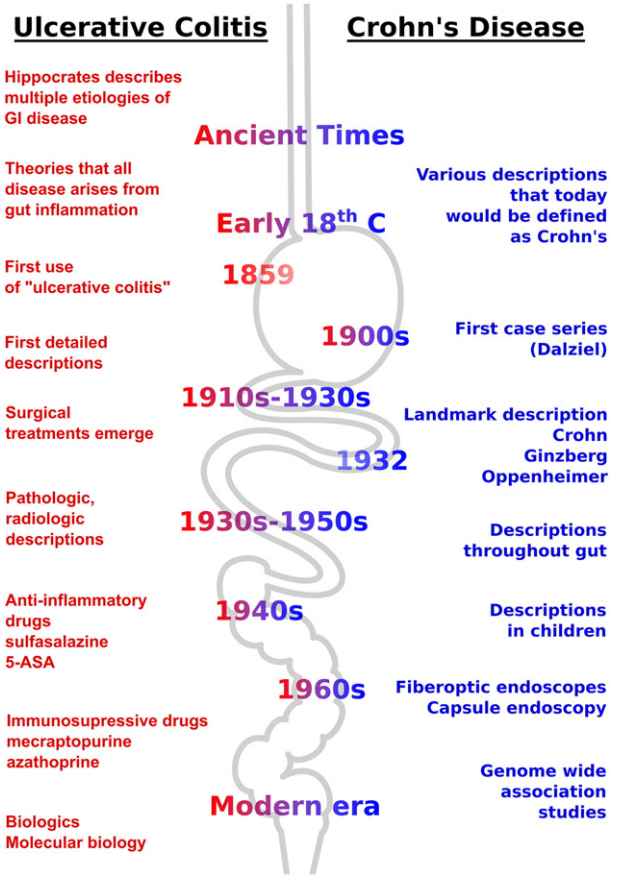

Figure 1 Approximate timeline contrasting major historical events in the understanding of ulcerative colitis (red) and Crohn's disease (blue).

2. Crohn's disease

2.1. Discovery and definition (ancient times — 1932)

CD was recognized as an entity separate from UC in 1932 with a publication by Crohn et al.[43] Today, CD is defined as a disease of transmural inflammation with skip lesions that may involve any part of the GI tract from mouth to anus. Additionally, as Fielding has pointed out, the initial 1859 case of UC reported by Wilks (discussed above) may not have been UC at all, but instead CD.[44] Indeed, others have uncovered many reports in the literature prior to 1932 that describe CD (often by the name of "regional ileitis" or "regional enteritis").[45,46] Notable descriptions prior to 1932 included those by Morgagni in 1769 and Dalziel in 1913. But just as Wilks' paper became the landmark UC description, Crohn's paper is recognized as the seminal report of CD.

The earliest complete description of CD likely belongs to Giovanni Battista Morgagni (1682–1771), who is often described as the 'father of anatomic pathology'.[47] Morgagni was known for his exactitude and precision, in both his dissections and his writing. One case report, in his treatise "The Seats and Causes of Diseases" (1761) describes a 20-year-old male patient who died following a longstanding illness of fever, abdominal pain, and bloody diarrhea. The autopsy revealed perforations and transmural inflammation with ulceration stretching from the terminal ileum to "two hands breadth" along the colon. The report also describes mesenteric lymphadenopathy and splenomegaly.[48]

The first series of CD cases was published in the *British Medical Journal* by Scottish surgeon Thomas Kennedy Dalziel (1861–1924), in 1913.[49] He described nine cases in which the pathologist observed eosinophils, giant cells and granulomas with no infectious agents. Dalziel describes the bowel as having "the consistence and smoothness of an eel in a state of rigor mortis." Two of the cases were fatal due to extensive disease and strictures. The remaining cases (including a 10 year old) had localized disease treated successfully with surgery ("one does not hesitate in resecting large portions of the intestine"). Dalziel also noted involvement of the colon in this disease, something that Crohn did not do. On the proposed name of the condition, Dalziel notes "my friends the pathologists prefer to call it hyperplastic enteritis."[49]

The landmark article that identified CD for the world written by Burrill B. Crohn (1884–1983), Leon Ginzburg (1898–1988) and Gordon D. Oppenheimer (1900–1974) was published in the October 1932 issue of the *Journal of the American Medical Association*.[43] They described a condition called "regional ileitis" in 14 patients, ranging in age from 17 to 52. The pathology consisted of chronic "necrotizing and cicatrizing inflammation" in the terminal ileum, as well as transmural inflammation, strictures and fistulas. Despite its fame, this article has been the subject of controversy.

The eponym of CD was ascribed to Crohn by way of a fascinating set of circumstances. According to Ginzburg,[50] he and Oppenheimer initially identified the pattern of disease and collected 12 cases, all of which had been patients of A. A. Berg, a senior surgeon at the same hospital (Mount Sinai Hospital in New York City). Apparently, Ginzburg and Oppenheimer wrote most of the manuscript and wanted to add Berg's name as an author; however, Berg refused, because he had not been previously involved in the project.[50] In an attempt to increase the number of cases in the report, Ginzburg and Oppenheimer were put in touch with Crohn by the pathologist Paul Klemperer. Crohn was given the manuscript and was not heard from again until it was published with two additional cases and Crohn's name first![50]

Crohn probably did not expect that the eponym would belong to him; the article's title proposed a name for the disease — regional ileitis. It is also unclear if Crohn submitted the manuscript to the journal with his name first. At the time, the journal's policy was to order the authors alphabetically by last name.[51]

2.2. Understanding a new disease (1932–1956)

During the 1930s and 1950s, CD was found to occur throughout GI tract. It was described in the esophagus,[52] stomach,[53] duodenum[54] and jejunum.[54] These reports probably worked against the initial names of this disease such as "regional ileitis" and "regional enteritis", and favored the evolution of the eponym for lack of a more precise medical term. This era also saw identification of CD in patients as old as 80[55] and many cases of patients under 10 years of age.[56] Charles Wells was the first to connect CD with skip lesions (an area of healthy bowel between two areas of diseased bowel).[57]

Wider recognition of CD by the general public likely coincided with President Eisenhower's surgery for CD in 1956.[58] At the time, he was 65 years old and had suffered from years of abdominal pain, but had only been recently diagnosed with CD. Following persistent right lower quadrant pain secondary to a bowel obstruction, he required an emergent operation in the middle of the night.[59] His openness about the disease and the surgery was instrumental in shifting CD from a medical curiosity to a relatively well-known disease.

2.3. The modern era (1957–present)

2.3.1. Scientific and therapeutic advances

Following World War II, a rapid increase took place in the number of RCTs for treatments of CD. The epidemiology of CD was also studied in great detail. After initial controversy, it became clear that CD is a disease that primarily affects individuals in industrialized countries[60] and that it was increasing in incidence.[61] The reasons for these phenomena are still not clear.

A 1960 paper by Hugh Evelyn Lockhart-Mummery (1918–1988) made the distinction between UC and CD in the colon.[62] H. E. Lockhart-Mummery was the son of John Percy Lockhart-Mummery, the distinguished colorectal surgeon who had pioneered the use of sigmoidoscopy in 1909 (see above).[63] Initially, the idea that UC and CD were separate diseases of the colon encountered much resistance. Even late into the decade, many prominent physicians, including Dr. Crohn himself, still did not believe that CD could affect the colon.[64]

As with UC, over the last 50 years, the understanding of CD has been revolutionized by immunology, genetics and molecular biology. One such strategy, the genome wide

association study (GWAS), is a method of screening entire genomes for connection with a particular disease. GWAS have been used in many fields of medicine since the first study of this type was published in 2005.[65] To date, this strategy has identified more than 50 polymorphisms that are connected to CD.[66] GWAS are delivering new insights into the genetic mechanisms of both UC and CD by helping determine disease susceptibility and also providing novel drug targets.[66,67] The results of these studies have also been used to subgroup patients into different disease phenotypes, which may eventually prove useful in predicting treatment response.[68]

Many of the CD trials conducted during the second half of the 20th century overlapped with UC and often included patient groups for both diseases. CD is treated with many of the same drugs as UC, including 5-ASA, corticosteroids, immunomodulators and biologics. One drug used to treat CD, but not UC, is methotrexate. Like the thiopurine drugs, methotrexate was developed as an anti-cancer drug in the 1950s.[69] Although multiple antimetabolite drugs were applied to UC in the 1960s, the first trial showing a clear benefit of methotrexate to CD patients did not appear until 1989.[70] Methotrexate inhibits folic acid metabolism, which is required for many cell functions, including purine synthesis. Thus, this drug acts as a powerful inhibitor of cell metabolism and mitosis. It too was honored in the 1988 Nobel prize.[71]

Over the past 20 years, medical therapy has focused on corticosteroids and immunomodulatory drugs. Now that translational research has highlighted the importance of TNF-α, biologics are coming to the forefront,[72] although the long term outcomes of these treatments are not yet known.[73,74] In addition to infliximab, another biologic drug for treating CD is the TNF-α inhibitor monoclonal antibody adalimumab.[75] Unlike the humanized murine antibody infliximab, adalimumab is of entirely human origin, meaning it is much less likely to cause adverse allergic reactions.[76] It is also likely that many more biologic agents will be available for the treatment of IBD in the near future.[77] Examples of biologics currently under investigation include: vedolizumab (inhibits leukocyte trafficking), tofacitinib (inhibits production of inflammatory cytokines) and ustekinumab (an interleukin-12 and -23 antagonist).[77]

As pharmacologic agents for IBD treatment have become increasingly sophisticated, non-pharmacologic therapies such as nutritional therapy and surgery have also changed over time.[78] Nutritional therapy has become increasingly important in the management of CD over the past 25 years. It was first noted in 1974 that CD patients treated for malnutrition prior to scheduled surgery had improved disease.[79] The use of nutritional therapy as treatment, not merely as supportive therapy is increasing through the use of supplements, enteral feeding and total parenteral nutrition, especially in children.[80–82] The role of surgery in IBD management has also changed as minimally invasive techniques have developed and complication rates have dropped.[83]

2.3.2. Modern technological advances

A drastic change to IBD medicine over the last 60 years is the contribution of new technology. Fiberoptic colonoscopy[84] with biopsies,[85] and ileocolonoscopy,[86] have revolutionized the diagnosis of both UC and CD worldwide, especially with respect to defining the extent and severity of disease. In 1982, Lee and Papaioannou published a report detailing the benefits of strictureplasty for nine patients with CD.[87] The attention to detail and follow-up of the cases in their series challenged the conventional wisdom that anastomosis of a bowel with active CD would lead to fistulae.

In 2001, the FDA approved a wireless 'pill camera' for capsule endoscopy. This untethered capsule is swallowed and travels through the entire GI tract obtaining digital images.[88] An entirely non-invasive version of an endoscopy has also recently been developed — virtual endoscopy. Computed tomography (CT) scans are used to reconstruct a three-dimensional digital model of the bowel, allowing a moderate resolution virtual tour of the GI tract on a computer screen.[89] Since the late 1990s, an extrapolation of this technique, using magnetic resonance image (MRI)-based virtual endoscopy has been used in preliminary and feasibility studies to identify features of CD.[90] MRI is also a safe, valuable tool for locating fistulas in patients with IBD.[91] Yet since it is not possible to obtain biopsies for histology with these non-invasive techniques, endoscopy is often still necessary.

2.3.3. Etymology

Eponyms, such as 'Crohn's disease', have long been criticized for their inaccuracies and a movement to abolish them is gaining momentum.[92] Experts in medical linguistics have proposed that, if used at all, the non-possessive form of all eponyms be used for "simplicity and technical advantages."[93] 'Crohn disease' is a term that has been used sporadically for decades,[94,95] although only recently has this use gained wide acceptance by academic journals and medical textbooks.

3. History as it happens — IBD in the 21st century

While they may be biologically separate diseases, UC and CD are united by the term 'IBD.' This grouping is certainly useful from a patient perspective. It allows for the combining of resources of support groups that have grown in strength since their inception in the 1970s.[64] Today, support groups, such as the European Crohn's and Colitis Organization (ecco-ibd.eu), the Crohn's and Colitis Foundations of America (ccfa.org) and Canada (ccfc.ca), operate around the world, connecting individuals with specialists and fellow patients. These groups also provide significant fundraising initiatives that support laboratory research, clinical trials and production of resources for patients and physicians. These organizations also make available numerous online resources that can be useful for patients and physicians alike — including IBD diet recipes and advice for traveling.

The history of IBD is rapidly evolving. New technology, such as the widespread use of smart phones, is changing its management. Smart phone 'apps' (many of which are freely available) are now available to patients to track diet and bowel movements — there is even an app from the Crohn's and Colitis Foundation of Canada called "Can't Wait" that uses the smart phone's built-in GPS to locate the nearest bathroom.

4. Conclusions

As a symptom cluster, IBD has likely existed for hundreds, if not thousands, of years, perhaps for all of human existence. Since its earliest descriptions as a disease entity, IBD has evolved from a commonly fatal disease to a manageable chronic condition with two broad types. Its history includes dedicated physicians, brilliant discoveries, and even some intrigue. Notwithstanding the many triumphs, the etiology of IBD and its cure are still unknown. There is much to be optimistic about though, since more is known about IBD than at any previous point in history and this knowledge continues to increase. The history of IBD is still being written.

Conflicts of interest

None.

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