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Ulcerative Colitis

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History of Ulcerative Colitis

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1.1 Introduction

Ulcerative colitis (UC) is an idiopathic inflammatory disease limited to the colon [1] that extends proximally from the rectum. It is a chronic condition which presents primarily in the third and fourth decades of life [2] with bloody diarrhea, rectal urgency and abdominal pain [3].

The incidence and prevalence of UC, along with Crohn's disease, is highest in westernized nations, such as Canada, Northern Europe and Australia. In recent years, a rise in the incidence and prevalence was observed in developing nations, probably related to a change in environmental risk factors, such as diet, microbial exposure, sanitation, lifestyle behavior, medications and pollution exposure [4].

Despite years of investigation, the roots of UC have yet to be identified. The strongest modifying factors known so far include: cigarette smoking [5]; appendectomy, which seems to have a protective effect [6]; family history of inflammatory bowel disease (IBD), which is the greatest risk factor for the development of UC and Crohn's disease [7].

1.2 Ancient Times

The earliest descriptions of chronic diarrhea date back to ancient Chinese medicine. In 722 BCE the yellow emperor's Canon of internal medicine described

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symptoms (abdominal pain, diarrhea, rectal bleeding) of a disease resembling UC [8]. In the 4th century BCE, the great Greek physician Hippocrates of Kos gave a description of a bloody, mucus-streaked stool [9] and, in the first century CE, Aretaeus of Cappadocia [10] noted a distinct type of "foul evacuation", occurring more often in women than in men. Even if both physicians recognized different forms of diarrhea, they could not differentiate between infectious and non-infectious causes.

1.3 Discovery

1.3.1 First Case Reports

It has been suggested that, in 1745, Prince Charles, the Young Pretender to the throne of Great Britain, suffered from UC and cured himself by adopting a milk-free diet [11].

In the 17th century the English physician Thomas Sydenham gave a detailed description of cases of "bloody flux", a condition characterized by the presence of blood mixed with loose, watery stools. This illness was probably of infectious origin, although it is impossible to verify whether instances of UC were included [12].

In the 18th century, another English physician, Burch, reported the case of a 40-year-old man who developed persistent "bloody flux" in 1756 and also experienced bouts of jaundice, fever and episodic abdominal pain 5 years later. In the following years he also experienced sore eyes and joint pain suggesting extra-intestinal manifestations. The symptoms continued intermittently until the patient died in 1774. The case report suggested the possibility of non-specific inflammatory bowel disease complicated by primary sclerosing cholangitis [13].

In 1793, in his *The Morbid Anatomy of Some of the Most Important Parts of the Human Body*, the pathologist Matthew Baillie (1761–1823) suggested that, according to his autopsy descriptions, people were dying from UC in the latter part of the 18th century [14].

In 1859, Samuel Wilks (1824–1911) of London was the first physician to use the term "ulcerative colitis" in a case report. The patient was a 42-year-old woman who presented with diarrhea and fever, which was initially diagnosed as arsenic poisoning. The autopsy showed transmural ulcerative inflammation of the entire colon and terminal ileum, initially designated as simple ulcerative colitis, but which was later revealed to be a case of Crohn's disease [15].

The 1875 case report of Wilks and Moxon, regarding a young woman who had died from severe bloody diarrhea and whose autopsy showed ulceration and inflammation of the colonic mucosa, was probably the first instance of UC [16].

Around the same period of time, similar reports circulated in Europe such as the description by William Henry Allchin (1846–1912) of London in 1885 of the extensive denudation of the colon in a young woman who died after 6 weeks of diarrhea [17] and a series of cases of "ulcerative colitis" published by Sir William Hale White of London (1857–1949). It is from this report that the term "ulcerative colitis" entered into the general medical vocabulary.

1.3.2 First Therapeutic and Diagnostic Attempts

Surgical management of UC began to emerge around the last decade of the nineteenth century.

In 1893, the English surgeon Arthur William Mayo Robson (1853–1933), Professor of Surgery at Yorkshire College of Victoria University attempted to treat the inflamed bowel of a 37-year-old female patient with bloody diarrhea by means of a temporary inguinal colostomy permitting daily irrigations with ipecacuanha and tincture of *Hamamelis* and, later, with a boracic acid solution, allowing the closure of the colostomy. This was performed using a left inguinal incision of the abdominal wall through which the sigmoidal colon was fixed and opened externally [18].

In 1902, Robert Fulton Weir (1838–1927) of New York was the first to perform an appendicostomy in a patient with UC to allow colonic irrigation with antimicrobial solutions (5% solution of methylene blue alternating with a 5% solution of silver nitrate or bismuth). Even if it did not achieve complete functional exclusion of the colon, Weir's appendicostomy remained the standard of care in severe colitis for years [19].

In 1907, John Percy Lockhart-Mummery (1875–1957) reported cases of carcinoma of the colon in 7 of 36 patients in his series of surgical cases of UC. In the same paper, he was the first doctor to demonstrate that the recently developed illuminated proctosigmoidoscope was a safe and invaluable tool for colonic mucosa evaluation and diagnosis.

1.3.3 1909 London Symposium

In 1909 the Royal Society of Medicine in London held a symposium where over 300 cases of patients admitted to London hospitals (Guy's, London St Bartholomew's, St George, St Thomas, St Mary and Westminster) from 1883 and 1908, with severe inflammation of the colon, were presented and discussed. The conference shed some light on different aspects of the disease, such as risk factors (early adult and middle age), common presenting symptoms (diarrhea and hemorrhage), complications (141 patients had died from perforation of

the colon, hemorrhage, liver disease, septic infection, pulmonary embolism and malnutrition) and therapeutic attempts. Medical treatment included a great variety of options, such as "slop diets", Sydenham's remedy (3 pints daily of milk soured by lactic acid), astringents, opium, tincture of *Hamamelis*, rectal instillations of boracic acid, silver nitrate or creolin administered to control a presumed infection.

The most popular operation at the time was appendicostomy or, if the appendix had been removed, a valvular cecostomy followed by colonic irrigations. Etiologic speculations focused mainly on bacteriological possibilities [20]. In March of the same year, the British Medical Journal published the Herbert P. Hawkins "Address on the natural history of ulcerative colitis and its bearing on treatment". This lecture read before the Bristol Medico-Chirurgical Society explained that "nothing can be done until the natural history of the disease is understood". He indicated that the active bacterial agents responsible for the disease should be found so that they could be controlled [21].

1.4 1910s–1950s

1.4.1 Breakthroughs and Growing Interest

In the decades following 1909, reports of cases of UC started coming in from all over the world and in 1913 at the Paris Congress of Medicine, the disease was one of the principal subjects discussed. In the same year, the first radiological appearance of UC was described independently by Sterlin and Kienbock, and the first American case report was published by Bassler of New York [22].

By the 1930s, the first descriptions of pediatric UC started to emerge, such as the 1923 Helmholz of Mayo Clinic report of the clinical features of the disease in five children aged 8 to 15 [23] and the 1940 Mayo Clinic report of a total of 95 children with UC [24].

The impact of UC on growth and sexual development in children was also recognized; in 1939, Davidson of the Bronx Memorial Hospital reported impaired growth in children affected by the disease and, in 1937, Welch et al. tried to explain nutritional deficiencies by demonstrating substantial fecal losses of proteins and electrolytes [25].

Several breakthroughs were made, such as the first demonstrations of familial predisposition to UC by Spriggs in 1934 and Moltke in 1937, who recorded five families with multiple instances of the disease (mother/daughter in two families; brother/sister in two families and father/daughter in one family) [26].

In 1915, another important milestone was reached with Hewitt's association

between chronic UC and polyps [27] and, subsequently, in 1948 when Wengensteen recognized that UC heralded colon cancer [28].

1.4.2 Medical Therapy

Medical interventions included several experimental treatments such as "organotherapy", which consisted of feeding raw porcine small bowel to patients in the hope of replacing a lack of a hypothetical factor [29]. Another treatment proposed was "ionization therapy", which involved irrigating the bowel with a zinc solution and then running an electric current through the solution [30]. Furthermore, in 1923, in his paper on UC, Strauss from Berlin suggested that a bland diet and blood transfusion could be helpful [31]. Psychogenic factors were formally implicated in UC in the reports of Murray and Sullivan who had been impressed with a chronological relationship between emotional disturbances and the onset of bowel symptoms in men and women with significant emotional disturbances involving their marriage, home life and interpersonal relationships. Psychiatric precepts during the 1930s and 1940s emphasized an UC personality described as "immaturity of the patient, indecisiveness, over-dependence and inhibited interpersonal relationships together with critical emotional events including the loss of a loved one, feeling of social rejection and maternal dominance".

Psychotherapy was an important part of medical treatment during the 1930s–1950s. Grace, Pinsky, and Wolff reported lower operability rates, fewer serious complications, and lower mortality rates in 34 patients with UC treated by stress control therapy. However, in a series of 70 patients with severe UC treated by psychoanalytically oriented psychotherapy for three months, no specific value was observed in preventing surgical intervention on severe recurrences. Years later, Feldman et al. found no evidence of a psychogenic causation in a controlled study of 34 patients with UC [32].

1.4.3 Surgical Treatment

Initially, surgical treatment of UC was sporadic and mostly experimental; however, after 1930, surgical interventions gradually became standardized. Several of these techniques were later abandoned, but a few are still in use today.

Some of these abandoned experimental surgical treatments included Neumann's description of pneumoperitoneum and Dennis's vagotomy as simple and effective therapeutic procedures in apparently intractable cases of chronic UC. In 1943, Neumann described seven cases of UC treated with therapeutic pneumoperitoneum. The technique consisted of inserting a needle

into the left iliac fossa, at one inch from the umbilicus, and inserting oxygen or air at a pressure of 2–3 cm water with the same apparatus already in use for pneumothorax; the procedure was repeated once or twice weekly for months until the patient had sufficient clinical relief [33]. In 1947, Dennis et al. reported the results obtained by a vagotomy performed on patients with UC. The technique consisted of dividing the vagal nerves by means of a seventh intercostal anterior space incision; the patients were followed up for months [34].

Surgical interventions which have withstood the test of time include ileostomy, and subtotal or total colectomy.

1.4.3.1 Ileostomy

The first surgeon suggesting ileostomy to treat UC was John Young Brown (1865–1919) who, in 1913, suggested that placing the large bowel on complete physiological rest was necessary for the treatment of the inflammatory bowel disease. Brown's procedure, in adjunct to cecostomy for bowel irrigation obtained after appendix removal, consisted of a complete division of the ileum near the ileocecal valve and a flush terminal ileostomy, protruding some centimeters and fixed in a mid-line laparotomy. The intestinal contents were kept away from the skin of the abdominal wall by a catheter sewn in place. After the patient had recovered sufficiently, the catheter was removed and the ileostomy "matured" as a result of serositis secondary to the caustic ileal contents [35].

Subsequently, many surgeons, including Brown, started to divert only the fecal stream with an ileostomy, without a stoma for irrigation purposes. This procedure also had the advantage of being reversible, by closing the stoma. It was also noted that, even after a prolonged large bowel rest, closing the ileostomy was often followed by a flare-up of the colitis.

Ileostomy according to Brown provided total fecal diversion, but presented a high rate of complications, such as dehydration, hydroelectrolytic disorders and skin excoriation in the short term, and mechanical problems in the long term (retraction, stenosis, prolapse, parastomal hernia). Furthermore, since this operation was undertaken with reluctance and was reserved for critically ill patients, it was associated with high mortality [36].

The use of ileostomy spread after the introduction of easier to manage devices and after the development of an alternative technique for fashioning the ileostomy as proposed by Sir Bryan Brooke in London.

Bryan Nicholas Brooke (1915–1998) Professor of Surgery at Queen Elizabeth Hospital in Birmingham described a new technique for everting ileostomy in order to minimize skin excoriation; it was adopted worldwide and continues to be used today. The procedure consisted of a partial intussusception of the external part of the ileal segment of the stoma, allowing protection of the serosa, and reducing stenosis and excessive output. It also facilitated the application of a closely approximated device to the base of the stoma, thereby

minimizing the ingress of fluid which could subsequently lead to leakage under the free edge of the stoma device [37]. Furthermore, in the late 1950s the birth and growth of stoma care was pioneered at the Cleveland Clinic in Ohio where the "R.B. Turnbull Wound Ostomy Continence (WOC) School" was born [38].

1.4.3.2 Ileorectal Anastomosis

Total colectomy with ileo-sigmoidal anastomosis for UC was first described in 1903 by Howard Lilienthal (1861–1946) [39] from New York who was, for the most part, known for his interest in thoracic surgery. In 1943, Sir Hugh Berchmans Devine (1878–1959) reported a multiple-stage procedure of partial colectomy and ileo-rectal anastomosis for patients in very poor condition [40]. Doctor Alfred A. Strauss (1881–1971) was an early advocate of the total proctocolectomy and end ileostomy as a definitive treatment for UC. After Strauss presented his results regarding this approach in 1944, it was clear that a multiple-stage procedure consisting of removing the entire colon and rectum was effective and safe in the management of UC. At the same time, the surgeon described the "Koenig Bag" a rubber device which could be bound and sealed to the skin and supported with an elastic belt, designed to prevent bowel contents from reaching the skin around the stoma. This device was named after Mr. Koenig, who had had an ileostomy for UC and helped develop the stoma bag for his own use [41].

In 1948, Richard Cattell (1900–1964) described a three-stage surgical approach: ileostomy, subtotal colectomy and, finally, an abdominoperineal resection of the rectum. In 1949 Miller recommended a two-stage ileostomy and proctocolectomy and, in 1951, Mark M. Ravitch (1910–1989), a leading pediatric surgeon and a pioneer in the United States in the use of mechanical stapling devices for surgery, accomplished the procedure in one stage. Furthermore, Ravitch was an innovator, introducing mucosectomy to the restorative surgical technique (sphincter saving in ileo-anal anastomosis) for managing UC. In 1951, Campbell Gardner (1908–1963) and Gavin Miller (1893–1964) presented a series of 69 patients, who had undergone a one-stage colectomy, consisting of ileostomy and colectomy at the same time. Due to the severity of illness of the study population, mortality occurred in 15% of cases [42].

Total colectomy with ileorectal anastomosis performed for the most part by Devine in Australia [43] and in a more systematic way in the 1950s by Stanley Osborn Aylett (1911–2003) in England did not require ileostomy, restoring intestinal continuity with ileorectal anastomosis. Aylett reported an operative mortality of 5%, and 90% of the patients were restored to health [44].

By contrast, because of the poor results in many patients, the need for additional surgery and the risk of cancer, many surgeons remained skeptical and reluctant to carry out the procedure [45].

1.5 1960s–1990s

1.5.1 Medical Therapy Milestones (Table 1.1)

1.5.1.1 Aminosalicylates

Sulfasalazine (SASP) was first synthesized by Nanna Svartz, a Swedish Professor of Medicine at the Karolinska Institute in Stockholm. It contains sulfapyridine (SP), an antibiotic, and 5-aminosalicyclin acid (5-ASA), an anti-inflammatory, linked by a diazo bond. Dr. Svartz initially used sulfasalazine to treat patients with rheumatoid arthritis, but the results were not encouraging. Unexpectedly when used in patients with UC it led to significant improvement in their diarrhea [46]. She published her first case report in 1942, followed by a large uncontrolled study in 1948, which showed that the majority of patients (70–80%) with mild–moderate UC responded well, but relapse was the rule at drug discontinuation [47]. The efficacy of sulfasalazine was confirmed by Baron in 1962 in the first double blind randomized control trial (RCT) [48] and SASP therefore became the drug of choice for UC all over the world. In 1977, Azad Khan and Sidney Truelove (1913–2002) recognized that the active therapeutic part of SASP was 5-ASA and that the SP functioned as a mere carrier and was also responsible for the majority of the side effects [49].

Another important turning point in the medical therapy of UC was realized by Massimo Campieri of the University of Bologna who demonstrated the superiority of rectally administered 5-ASA to placebo, rectally administered

Table 1.1 Timeline of major historical events in the medical treatment of ulcerative colitis

Year	Author	Active compound
1948	Svartz	Oral sulfasalazine
1955	Truelove	Oral corticosteroids
1962	Lennard-Jones	Topical corticosteroids
1962	Bean	6-MP
1974	Truelove	Azathioprine
1977	Azad Khan	Oral 5-ASA
1981	Campieri	Topical 5-ASA
1994	Lichtiger	Ciclosporin
2005	FDA approved	Infliximab
2012	FDA approved	Adalimumab
2013	FDA approved	Golimumab
2014	FDA approved	Vedolizumab

steroids and oral 5-ASA for the induction of symptomatic, endoscopic and histological improvement and remission [50]. Seventy years after Nanna Svartz's discovery of SASP, salicylates continue to play a central role in the treatment of UC. The few side effects, the relatively low cost and effectiveness make these drugs still competitive even in the era of biological agents. The new oral formulations, by improving patient compliance and allowing treatment of left-sided colitis, may open new horizons for an old drug [51].

1.5.1.2 Corticosteroids

In 1954, Palmer and Kirsner published their experience with corticosteroid use in 120 patients with UC, demonstrating that corticosteroids were able to induce a very rapid symptomatic response but, on the other hand, the authors were unable to induce permanent healing. Of their 120 patients, 35 went into remission (defined as complete resolution of symptoms) and another 57 patients improved. In addition to the clinical effects, the common side effects of corticosteroids were reported (acne, hirsutism, Cushing deformities, hyperglycemia, hypertension and an increased incidence of common and opportunistic infections, the latter being the cause of one death from overwhelming sepsis) [52].

In 1955, Sidney 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 the control subjects. Notably, this very first trial already included some type of rudimentary serial sigmoidoscopic assessments (defined as "normal", "improved" or "no change or worse") in their outcome measures [53].

In 1962, Professor John Lennard-Jones and Sir Francis Avery Jones (St Mark's Hospital, London) published the results of the first double-blind placebo-controlled trial of topical steroids in UC (proctitis). They used both symptomatic and sigmoidoscopic assessment to evaluate outcome and found significant improvement in the patients given steroids topically compared with placebo [54].

A turning point in the management of UC was the 1974 Truelove and Jewell definition of a 5-day intensive intravenous regimen for the treatment of severe attacks of UC. This regimen gave a higher remission-rate than that previously recorded, and failure to respond provided a simple and straightforward indication for surgery without further delay. Finally, early surgery and strict collaboration between the gastroenterologist and the surgeon dramatically reduced mortality [55]. Corticosteroid therapy in new intravenous, oral and topical formulations is still currently in use nowadays.

1.5.1.3 Thiopurines and Ciclosporin

In the 1960s, Bean et al. discovered that mercaptopurine (6-MP) was efficacious in patients with UC [56] and, in the 1970s, azathioprine, another drug of the thiopurine family, was also shown to be effective for treating UC [57]. An

unfortunate disadvantage of this particular family of drugs is the risk of complications from bone marrow suppression. In the 1980s it was found that patients with the enzyme methyltransferase (TPMT) were especially at risk for such complications due to decreased drug inactivation. Thus, TPMT gene variation is increasingly being measured in patients before starting azathioprine or 6-MP.

In 1994, intravenous ciclosporin was introduced as the first rescue therapy in patients with severe corticosteroid-resistant UC [58].

1.5.2 Surgical Milestones (Table 1.2)

1.5.2.1 Continent Ileostomy of Kock

A continent ileostomy (known as the Kock pouch) was proposed by Nils Kock in 1969 as an alternative to conventional end ileostomy in order to improve the quality of life of people in whom, despite the great improvements achieved with everted Brooke's ileostomy, physical and psychological difficulties were still common. It consisted of an internal ileal reservoir which stores stools and gas, a stoma outflow and outflow tract needed to intubate and evacuate the content of the reservoir, and a biologic valve interposed between the other two components to act as a pressure barrier to maintain continence. The long-term complications of Kock's pouch were mainly related to the valve mechanism: sliding of the nipple valve, fistula, partial or total prolapse of the valve, necrosis of the valve or the outlet, stricture of the stoma and inflammatory changes in the reservoir

Table 1.2 Timeline of major historical events in the surgical treatment of ulcerative colitis

Year	Author	Surgical procedure
1913	Brown	Ileostomy
1943	Neumann	Pneumoperitoneum
1944	Strauss	Total proctocolectomy and end ileostomy and Koenig Bag
1947	Dennis	Vagotomy
1951	Ravitch	One stage ileorectal anastomosis and ileostomy and mucosectomy
1952	Brooke	Brooke's ileostomy
1953	Turnbull	Stoma care
1966	Aylett	Ileorectal anastomosis without ileostomy
1969	Kock	Kock pouch
1980	Parks and Nicholls	S-pouch
1980	Utsunomiya	J-pouch
1995	Fazio	IPAA

(pouchitis) [59]. Continent ileostomy itself, developed as a fashioned form of the reservoir, led to the "pouch" concept and gave rise to the procedure of ileal pouch-anal anastomosis (IPAA) of the 1980s.

1.5.2.2 Ileoanal-anastomosis and IPAA

Ileoanal anastomosis has naturally evolved as a procedure for eliminating rectal disease in UC while maintaining intestinal continuity and preserving anal continence. A sort of gross ileoanal anastomosis was attempted as early as 1900 but functional outcome was very poor [60]. The first official attempt at the procedure was performed by Dr. Rudolph Nissen (1896–1981), a pioneer surgeon of his years, today remembered for the development of esophageal surgery (laparoscopic Nissen fundoplication). In 1933, Nissen performed a total proctocolectomy with ileoanal anastomosis on a 10-year-old child with polyposis and reported great postoperative results [61].

In 1947, Mark Ravitch (1910–1989) and David Sabiston at Johns Hopkins Hospital, executed "anal ileostomies", first in dogs and later in two patients with UC, describing very successful results. Ravitch was an innovator, introducing mucosectomy to the surgical management of UC. He performed mucosal stripping from the remnant rectum, leaving a 2–3-inch long rectal muscular cuff [62]. In the early 1960s, he was one of the first American surgeons to introduce mechanical stapling devices, first developed in Europe, for surgical use in the United States.

In 1951, John Cedric Goligher (1912–1998) of Leeds developed the loop ileostomy to protect the healing ileoanal anastomosis [63].

In a Journal of the American Medical Association (JAMA) paper of 1952, Dr. Russell Best reviewed the literature on patients undergoing colectomy with ileo-anal anastomosis and reported that, despite the overall feasibility of the operation, there were numerous complications, particularly sepsis and anastomotic leaks. He also noted that bowel function improved over time as the distal ileum dilated [64].

In 1955, in order to reduce stool frequency and avoid fluid imbalance, Miguel A. Valiente and Harry E. Bacon performed a triple-limbed ileal pouch combined with an ileoanal anastomosis on seven dogs. Five dogs died, but two had satisfactory results, sphincter control preserved with low stool frequency, formed consistency and minimal perineal irritation [65].

In the 1970s–1980s, Sir Alan Guyatt Parks (1920–1982) and Ralph John Nicholls (b. 1943) from St. Mark's Hospital reported their experience with 21 patients who were treated with an ileal-reservoir anal anastomosis for both UC and familial polyposis. Parks' version of the ileal-reservoir consisted of the S-pouch, sutured to a denudated anus (mucosectomy was performed), with a temporary loop ileostomy. His patients had a 70% complication rate which soon decreased to about 20%. Ninety percent of patients had no trouble with mucus leakage, and they were all continent [66].

About the same time, J. Utsunomiya at the Tokyo Medical and Dental University described different types of anastomosis, each having a temporary loop ileostomy. However, the J-shaped reservoir rapidly gained favor due to its simpler construction and its favorable functional outcome, including spontaneous evacuation of the neorectum [67].

The 1980s showed great promise for the ileal pouch-anal anastomosis. With a better understanding of the rectal anatomy and improvement in surgical staplers, great progress was made in treating UC. Surgical staplers, in particular, permitted easier and faster transanal anastomosis (double-stapled technique), thus avoiding the need for mucosectomy; the procedure became more accessible for dedicated surgeons and began to spread worldwide.

A significant milestone in restorative proctocolectomy with IPAA was Dr. Victor Warren Fazio (1940–2015) from Cleveland Clinic Foundation's description of 1005 patients who underwent double-stapled J-pouch surgery.

In 1995, Fazio and his team found that even though early (such as small bowel obstruction, wound infection, pouch abscess and pouch bleeding) and late (such as pouchitis and anal stricture) complications were common, restorative proctocolectomy with an IPAA was a safe procedure, with low mortality. Although the total morbidity rate was appreciable, functional results were generally good and patient satisfaction was high. Therefore, the operation was considered successful and safe for the majority of patients and represented the gold standard for the surgical treatment of UC [68].

1.5.3 Knowledge of Ulcerative Colitis in Italy

Studies on UC in European countries (especially in Britain) during the 1950s aroused great interest and led to vast literature. At the same time in Italy, there were only a few limited contributions. In 1958, for the first time in Italy, Professor G. Placitelli of Bologna gave a lecture on UC in Genova for the Italian Surgical Society (SIC). Medical and surgical interest in UC grew rapidly in Italy, Bologna being the main school in this subject [69] (Fig. 1.1).

1.6 Ulcerative Colitis Therapy in the Modern Era (2000s–today)

A major evolution in medicine in the last 20 years has been the application of molecular biology and genetics to the understanding of disease. The massive amount of data serves as a testament to its complexity and ever-elusive etiology. Molecular techniques have revealed that cytokine tumor necrosis factor-alpha (TNF-α) plays a role in the IBD inflammatory process. Thus, anti-TNF-α

Fig 1.1 Cover of the pioneering Italian book on ulcerative colitis published by Franchini and Possati in Bologna in 1960 [69]

monoclonal antibodies have been developed to inhibit the action of TNF-α.

The first anti-TNF approved by the Food and Drug Administration (FDA) for the treatment of UC in 2005 was infliximab [70], a chimeric monoclonal antibody biologic drug which proved to be an effective alternative treatment option for patients with moderate to severe disease who had had an inadequate response to conventional glucocorticoid treatment.

In September 2012, the FDA expanded the approved use of adalimumab for the treatment of moderate-to-severe UC in adults. Adalimumab is a fully human IgG1 monoclonal antibody directed against TNF-α, administered subcutaneously. The ULTRA 2 trial confirmed the efficacy of adalimumab (induction dose 160 mg/80 mg at week 0 and week 2, followed by 40 mg every other week) for both induction and maintenance of remission [71].

The PURSUIT-SC and PURSUIT-maintenance trials introduced a third anti-TNF agent exclusively for the treatment of UC: golimumab [72], which received approval from the FDA in 2013.

Vedolizumab, a humanized monoclonal antibody directed against the α4β7 integrin, has recently entered the market as the first anti-integrin biological for the treatment of UC.

The GEMINI 1 study has evaluated the efficacy of vedolizumab for the induction and maintenance of remission in active disease. The results of the trial were impressively positive, even in the anti-TNF-experienced subgroup [73].

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