REVIEW

THE GENESIS OF INFLAMMATORY BOWEL DISEASE YESTERDAY, TODAY, TOMORROW

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SUMMARY

The discovery of Inflammatory Bowel Disease (IBD) has had a tumultuous trajectory, beginning with its recognition as a medical entity to defining and understanding. The genesis of the two diseases included in the spectrum of IBD is the same with the one of humanity, the earliest descriptions belonging to ancient Greeks, but the differentiation between them and other intestinal pathologies took place years later. Even establishing the names of Ulcerative colitis (UC) and Crohn’s disease (CD) encountered difficulties. With the beginning of the modern era, remarkable progress has been made in the field of medicine - both in understanding the diseases and in treating it. Outstanding medical and surgical techniques have led to significant improvement in prognosis and quality of life, so nowadays IBD is no longer seen as a medical curiosity but as a manageable chronic condition. This article is a review of the history and treatment of Inflammatory Bowel Disease up to the present time, when, despite all the advances made, the etiopathology and cure remain unknown. Key words: inflammatory bowel disease, ulcerative colitis, Crohn’s disease, regional ileitis, history

La genèse de la maladie inflammatoire de l’intestin hier, à présent, demain

La découverte de la maladie inflammatoire de l’intestin (MII) a eu une trajectoire tumultueuse, en commençant par sa reconnaissance comme une entité médicale à la définition et la compréhension. La genèse de ces deux maladies incluses dans le spectre de l’IBD est la même avec celle de l’humanité, les premières descriptions appartenant aux Grecs anciens, mais la différenciation entre eux et d’autres pathologies intestinales a eu lieu des années plus tard. Même établir les noms de rectocolite hémorragique (RCH) et la maladie de Crohn (CD) a rencontré des difficultés. Avec le début de l’ère moderne, des progrès remarquables ont été accomplis dans le domaine de la médecine - à la fois dans la compréhension des maladies et leur traitement. D’éminentes techniques médicales et chirurgicales ont conduit à une amélioration significative dans le pronostic et la qualité de vie, ainsi que de nos jours MII n’est plus considérée comme une curiosité médicale, mais comme une maladie chronique gérable. Cet article est une revue de l’histoire et du traitement des maladies inflammatoires de l’intestin à l’heure actuelle, car, en dépit de tous les progrès réalisés, l’etiopathologie et la guérison restent inconnus. Mots clés: maladie inflammatoire de l’intestin, rectocolite hémorragique, maladie de Crohn, iléite régionale, l’histoire

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Ulcerative Colitis - First there was darkness!
From discovery to definition

Through the ages there have been numerous controversies regarding the nomenclature and etiopathogenesis of IBD. Dr. J Arnold Bargen (who worked at Mayo Clinic and was the President of the American Gastroenterological Association) maintained in 1966 that “as long as the cause of UC remains unknown, defining the disease would be impossible and shouldn’t even be attempted”. Nevertheless, subsequent advances have made defining the disease as truthfully an
imperative need as possible. UC is a chronic inflammation of the colon (large intestine) lining, of unknown cause, often characterized clinically by blood in stool, diarrhea, rectal tenesmus and abdominal pain, by ongoing involvement of the mucosa, and a centripetal extension from rectum up to the cecum [1].

UC is the first disease among those included in the IBD spectrum that was defined as a distinct entity. The early history of IBD begins with the history of UC, nonetheless that is not to say that UC predates CD - both diseases had afflicted patients long before modern medicine was able to discover and define them [2]. The first description of UC still remains a matter of controversy. Starting with Greek antiquity, there have been mentions of chronic noncontagious diarrhea - Hippocrates himself (460-370 BC) discussed the possible etiology of diarrhea [3]. Several other reports of the disease were subsequently attributed to Soranus (117 AD) and Aretaeus of Cappadocia (300 AD) [4]. Although the name of UC is not entirely accurate – insomuch as ulcera- and Aretaeus of Cappadocia (300 AD) [4]. Although the name of UC is not entirely accurate – insomuch as ulcers are not necessarily present, and as the disease quite often involves the rectum and the sigmoid colon - it became widely accepted [1].

The 19th century medical school of thought increasingly concerned itself with intestinal inflammation – Prof. Francois Joseph Victor Broussais 1772-1838 (professor of general pathology of the Academy of Medicine) and Dr. John Brown 1810-1882 (Fellow of the Royal College of Physicians of Edinburgh) supported the theory that all diseases derive their cause from the GI tract inflammation, a theory reinforced by the advent of the microscope, with its importance for entomological examinations [5]. The cholera epidemics raging at that time worldwide drew attention to the transmissible causes of diarrhea [6].

Although it was suggested that in 1745 young Prince Charles (known in Britain as The Young Pretender) developed bloody diarrhea following his defeat at the Battle of Culloden and was cured from UC by a milk-free diet, [7] Dr. Samuel Wilks (a physician at Guy’s Hospital London) is the one credited with the first description of the disease in 1859, when he identified it as being distinct from bacillary dysentery and named it idiopathic colitis [8]. He, as well as Dr. Walter Moxon (1875) (a physician at Guy’s Hospital and a lecturer in comparative anatomy and pathology) and Dr. William Henry Allchin (1885) (a physician and a lecturer in comparative anatomy, physiology, pathology and medicine at Westminster Hospital) afterwards outlined the clinical and pathological features of the disease: severe extensive colon inflammation with areas of dilated or narrowed lumen [9].

In 1888 Sir William Hale White (a physician at Guy’s Hospital, president of the Association of Physicians of Great Britain and Ireland and of The Royal Society of Medicine) published in London a detailed description of his UC cases, dismissing all the other causes discussed earlier: bacterial overgrowth, dysentery, tuberculosis, typhus etc. From that moment on, the UC entered the general medical vocabulary [10].

1909 was an important year in the history of UC. In January, at a symposium held by the Royal Medical Society in London, 317 cases recorded in London hospitals were reviewed – they revealed many important observations regarding: risk factors, disease onset symptoms, treatment attempts (antiseptics, antidiarrheal, sedatives, tried with no real benefit) [11]. Dr. John Percy Lockart Mummy (a surgeon at St. Mark’s Hospital, Hunterian Professor at the Royal College of Surgeons, the first secretary of the British Proctological Society) proved the same year that sigmoidoscopy was a safe method of evaluating and diagnosing the intestinal involvement, while in March the British Medical Journal published the work of Dr. Herbert P. Hawkins (St. Thomas Hospital) that confirmed the chronic and relapsing nature of the disease and its insidious onset with mild, often unnoticed bleedings, accompanied by constipation [12].

Later on, Sir Arthur Hurst (a neurologist at Guy’s Hospital, a pioneer in the diagnosis and treatment of psychoneuroses, who introduced the term dyschezia) proposed a more elaborate description of UC, including the sigmoid colon changes (muscular tension and stretching), as well as its distinction from bacillary dysentery. Although its etiology remained controversial, infectious or psychosomatic factors were taken into consideration as possible primary causes [13].

Ulcerative Colitis – And then there was light!

New treatments and curiosities

From 1909 onwards, as the decades passed, the medical community was making advances in their knowledge about UC. These included the detailed descriptions of familial predisposition made by Dr. Richard Lewisohn (known for the storage of blood in blood banks, who worked at Mount Sinai Hospital), the association of UC with colon polyps described by Dr. Hewitt JH. (a physician in Cleveland) and Dr. Owen H. Wangensteen’s (a surgeon at Minnesota Hospital - the developer of the suction apparatus, 1931) observation that UC can lead to colon cancer. Helmholtz, in 1923, was the first to describe UC in children (ages 8 to 15) [2].

Treatments were also making progress, with ileostomy and blood transfusions validated as useful means of therapy in UC. At first, the surgical treatment of UC was used infrequently and mostly in an experimental manner, but starting with the 1930s the surgical approach gradually became the standard of care. Some of the therapeutic practices were abandoned over time (therapeutic pneumoperitoneum, appendicectomy, pelvic autonomic neurectomy, thymus resection, vagotomy), but others have stood the test of time and are still in use to this day: ileostomy, partial or total colectomy [14]. Medical approaches also ranged from benign to unusual ones, to say the least: administering porcine raw small intestine (the so-called organotherapy), Dr. Thomas Sydenham’s (a physician in London, known as the “English Hippocrates”) therapy (3 glasses per day of milk soured with lactic acid), opium, silver nitrate, kerosene, ionizing therapy, hypnosis, hot water enemas, vaccines and extracts prepared from animal intestines, irigography using a zinc solution and...
an electrical impulse sent through it. [18] This period (1934-1944) also saw the first retrospective epidemiological study on UC, performed in Rochester, Minnesota, that revealed an incidence rate of 6 to 100,000 [15].

From the 1940s onwards medical interest in UC extended to all specialties. Thus, Dr. Shields Warren and Dr. Sheldon C. Sommers (who worked together at New England Deaconess Hospital, Laboratory of Pathology, in Boston) published the first ample description of UC pathology, with photographic and micrographic illustrations of vasculitis, cryptitis, distrophies and abscesses [16].

Radiology was increasingly being used to evaluate the disease extension and identify strictures [17]. Although the etiology of UC still remains unknown, that decade saw numerous attempts at solving this problem. The best-known theories took into consideration an infectious cause (Mycobacterium tuberculosis - Dr. Thomas K. Dalziel, Dr. J.A. Bargen's diplostreptococcus (Mayo Clinic), parasites, fungi and viruses – Dr. Fradkin 1937 - Entamoeba Hystolitica), Dr. Richard Henderson with Dr. Henry Pinkerton and Dr. Louis Moore (1942 - fungus - Histoplasma Capsulatum), Dr. Victor R.J., Dr. Kirsner J.B. and Dr. Palmer W. (1950 - viral etiology), an allergic (cow’s milk - Dr. Andersen was the first in 1925, then Dr. Truelove and Dr. Taylor in 1961 at Radcliffe Infirmary, Oxford) or dietary one (carbohydrates, fats), a metabolic one (mucinoses - elevated lysozyme in stools, Dr. Meyer K. and his colleagues Dr. Gellhorn A. and Dr. Prudden J. F. in 1947 at the New York Hospital), an autoimmune (anti-colon antibodies - Dr. Ove Broberger and Dr. Peter Perlmann were the first to sustain the hypothesis in 1959) or a toxic one (diets rich in sulphur compounds – Professor Dr. W. E. W. Roediger, Department of Surgery at Queen Elizabeth Hospital, toothpaste components – Dr. Powell J. J. in the 1990s) [1,18].

Also from an etiologic point of view many works of psychiatry supported the link between UC and psychiatric pathology - Winkower's study showed that 28 out of 40 UC patients had suffered a major emotional trauma before disease onset. Psychotherapy was deemed capable of solving some UC cases and of contributing to the remission of others [1,19].

It is well known nowadays that the symptoms of IBD can cause major psychological distress and there is proof that emotional factors have a crucial role in maintaining and prolonging disease flare-ups. Current treatment guidelines encourage doctors to deal with the psychosocial aspect of the disease, as well as with the organic one [1,20].

**Ulcerative Colitis –What can we do today?**

*Treatment and immunophysiology in the modern medical era*

After World War II, randomized clinical studies became widely used, ushering in the era of evidence-based modern medicine, and thus discarding local or systemic empirical therapies and vaccines without any benefit [2]. A major conceptual change was brought on by the accidental discovery, in 1940, of Swedish doctor Nanna Svartz (professor at Karolinska Institute of Pathology in Stockholm) of the impressive symptomatic remission of UC when treated with sulphasalazines – in her attempt to treat the King’s (Gustav V) arthritis, Svartz synthesized a new drug by the chemical linking of sulphapyridines with 5-amino salicylic acid and she noticed symptoms improving in patients with arthritis and UC. She also found similar changes in the connective tissue underlying the muscularis mucous lining and the articular connective tissue, but she thought that the therapy had worked through a bactericidal effect and she held the streptococcus responsible for the pathogenesis of both rheumatoid arthritis and UC. The clinical trials undertaken at the University of Chicago after 1940 and those led by Prof. Klotz U. (Institute of Clinical Pharmacology in Stuttgart) in 1970 proved the inefficiency of sulphapyridines and the low bactericidal activity of sulphasalazines. The 5-ASA derivatives (mesalazine, mesalamine) are still in use today due to their antiinflammatory and antichemotactic properties, their capacity for inhibition of lymphocyte activation and superoxide and hydroxyl radicals formation [14].

The discovery by Dr. Phillip Hench (professor rheumatologist) et al. (Dr. Charles Sloucumb, MD and Dr. Edward Kendall, Ph.D., from the Department of Biochemistry of the Mayo Clinic) in 1950 of the adrenocorticotrophic hormone (ACTH) (that brought them the Nobel Prize), and the subsequent development of glucocorticoid hormones – cortisone, prednisone, ushered in the era of steroid therapy of IBD. The remarkable short-term results of ACTH therapy even led some to consider a possible corticoid deficit as an etiologic alternative. In 1955 Professor Sidney Charles Truelove (from the Nuffield Department of Clinical Medicine - University of Oxford, to whom we owe the first prognostic classification of colitis) and Professor Leslie Witts (who invited Dr. Truelove at Oxford in 1947) published in the British Medical Journal the first blind controlled study that proved disease improvement and lower mortality in the corticosteroid treated group when compared to the control group [14,21].

The discovery of the double-stranded DNA helix by Drs. James Watson and Francis Crick in 1950 signaled the beginning of the genetic research era. Over the following decades it was the science of immunology that concerned itself most with the pathogenesis of UC. In the 1960s, Dr. Bean in Australia discovered that 6MP - an immunosupressive drug- is effective in UC by inhibiting DNA synthesis, in particular in those cells with a high mitotic rate, such as inflammatory cells [22]. In 1966, Dr. Bowen G. E. and Professor Dr. Kirsner Joseph Barrett (at the University of Chicago- he was the first to document the increased risk of colon cancer in IBD) compared the efficiency of a similar chemical compound – azathioprine, determining also the adequate dosage needed to prevent its adverse effects and proving its success in eliminating
the need for steroid therapy, partially or even completely [23].

In the last 60 years there has been a major breakthrough in medicine on our understanding of IBDs, due to the impact of molecular biology and genetics. The numerous data offered by these two fields of research give evidence of the complexity and elusive nature of their etiology [2]. Molecular investigations have proven TNFα to be a key factor involved in the inflammatory pathways of intestinal diseases, thus leading to the development of biological drugs – monoclonal anti TNFα antibodies, increasingly used nowadays in the treatment of severe forms of inflammatory bowel disease, in which the need for steroid therapy, partially or even completely [23].

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Klemperer. Dr. Crohn apparently took the manuscript and was not heard of for two years, after which he published the article including two additional cases (a 16-year-old boy and his sister) and with him as first author. Dr. Crohn possibly never expected the disease to receive this eponym as the article’s title had actually suggested the name of “regional ileitis” for it. But the publishing policy at that time was to list the authors alphabetically by their last name [35].

The difference between Dr. Dalziel’s 1913 article and the 1932 article was of timing and publicity: Dr. Crohn’s paper was presented to a large medical audience whose interest had already been awakened and it was afterwards published in the Journal of the American Medical Association, while Dr Dalziel’s work in the British Medical Journal was forgotten [35].

**Crohn’s disease - and then there was light!**

*Understanding a new disease (1932-1956)*

During this time CD was diagnosed along the entire GI tract – esophagus, stomach, duodenum, jejunum, ileum and colon - these findings giving support to the term CD and making the terms “regional ileitis or enteritis” inadequate [2]. Also, a few retrospective studies were completed during this period, such as a first one in Rochester, Minnesota, that showed an annual incidence of 1.9 per 100,000 residents between 1935 and 1954 [36]. There was a single study done in Europe, namely in Cardiff, United Kingdom, that showed a 0.2 per 100,000 per year incidence rate between 1935 and 1945 [37].

Dr. Charles Wells (in 1952, Liverpool) was the first to describe the lesions caused by the disease as “skip lesions” - that is, an area uninvolved by the disease, flanked by two involved areas [38].

An even wider recognition gained the disease after President Dwight D. Eisenhower’s (the 34th President of the United States) surgery for CD in 1956. His openness about his affliction helped turn this previously medical curiosity into a relatively well-known and important clinical entity. That year, at the age of 65, nine months after having suffered a myocardial infarction and after years of enduring abandomal pains because of which he had gone through an appendectomy in 1923, he showed radiological signs of regional enteritis and underwent emergency surgery for ileus [39].

**Crohn’s disease - what can we do today?**

After World War II, clinical trials and epidemiology gained a lot of interest and offered new insights into the disease: CD was found to be more prevalent in developed countries and to be rising in incidence; at the same time, relatives of patients with CD were found to be at a greater risk of developing the disease themselves [31].

In 1960, Sir Hugh Evelyn Lockhart-Mummery (a surgeon at St. Thomas Hospital at that time) - the son of the surgeon that had introduced sigmoidoscopy in 1909 – made the distinction between UC and CD involvement of the colon, although many doctors, including Dr. Crohn himself, disagreed that CD could affect the colon [40].

In the past 50 years our understanding of CD has been revolutionized by the advances made in the fields of immunology, genetics and molecular biology, which have led to the discovery of over 50 genome polymorphisms linked to the disease, that determine different phenotypes with distinct prognosis [41].

Unlike UC, CD was found to be effectively controlled by Methotrexate - the study published in 1988 that proved it also won the Nobel prize [42]. Alongside the biological therapy with Infliximab, Adalimumab is a newer biological agent, fully human and with fewer adverse reactions that is also in use in CD. Many other biological drugs are currently being developed or approved: Tofacitinib (it inhibits cytokine synthesis), Ustekinumab (IL-12 and IL-23 antagonist), Visilizumab (anti-CD3), Natalizumab, Vedolizumab (anti alpha4 integrins), Certolizumab, Golimumab (anti TNFalpha) [43].

Apart from the recent pharmacological studies and therapies, the nonpharmacological treatment means, such as nutrition and surgery, have become increasingly important over the last 25 years. The use of the nutritional approach as treatment and not just as a supportive measure has had obvious benefits, not just by decreasing malnutrition in children, but also by improving control of the disease activity and by helping the recovery after the surgical treatment. Gastroenterologists and surgeons alike, increasingly convinced by the futility of extensive intestine resections, started acknowledging the nutritional and physiological importance of preserving the integrity of the small intestine as much as possible [14].

The future is yet to come!

**Advanced modern technologies**

Since endoscopy plays an essential part in the management of IBD, the technological advances of the last 50 years (the development of fiberoptic endoscopy for colonoscopies and ileoscopies) have allowed for better biopsy assessments of the extension and severity of the disease [44]. After the video capsule was approved in 2001 by the FDA, new techniques have been developed - single and double balloon-assisted endoscopy, spiral enteroscopy – so as to surpass the limits of the video capsule and push enteroscopy [45]. The progresses made in the imaging techniques used in endoscopy have also enabled doctors to visualize mucosal fine details, tissue features and cellular alterations. These techniques – chromoscopy, magnification endoscopy, confocal laser endomicroscopy and endocytoscopy, narrow band imaging – have radically changed the medical management with regard to diagnosis, patient follow-up and treatment decision making.

As non-invasive methods of virtual endoscopy, computed tomographies and IRMs have proven their usefulness in the evaluation of the transmucosal involvement and its extension and of the disease complications: fistulae, abscesses, stenoses [45]. Optical coherence tomography is a new technique that offers real time cross-sectional subsurface imaging at a high resolution – 10 to
25 times higher than that of the preceding techniques – that would allow for a more accurate prediction of the malignant infiltration of the submucosa [46].

**IBD in the 21st century**

Despite of being two distinct diseases with different features, they are united under the IBD designation, that can be used as reference by patients in the entire world in search for support groups and the resources they offer (European Crohn’s and Colitis Organization ecco-ibd.eu, Crohn’s and Colitis Foundations of America and Canada ccca.org, cccf.ca) [2]. All the information sources, from news channels, books, multimedia to search engines and dedicated support lines, aim to provide advice to patients and their families regarding lifestyle, voyage recommendations, recipes and diets; they also connect patients with foreign medical specialists and offer the necessary psychological support so that they can lead as normal a life as possible. [47]. Special consideration is given to the management of the disease in case of pregnancy or of female patients of reproductive age so that there is no major disease impact on family planning [48].

Of the modern technologies, the smartphone finds good use in the management of IBDs: there are free apps for patients looking for diets, apps that highlight irritable foods « Low FODMAP Diet App », that help patients to monitor their diet and weight « Livestrong’s Calorie Tracker », that help them to keep record of their symptoms « My Pain Diary » and also an app that uses the smartphone GPS to track down the nearest restroom « Can’t Wait ».

**Conclusion**

In spite of all these remarkable technological progress and medical care advances with positive impact on prognosis, the etiology and definitive treatment of IBDs still remain largely unknown. The current treatment of IBDs, although much improved compared to its historical counterparts, remains supportive rather than curative. Dating back thousands of years, possibly since the beginnings of human existence, IBDs have evolved from fatal illness to two distinct chronic diseases that can be kept under control and that are being increasingly better understood and known. The history of IBDs is therefore still in the making.

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**Conflict of interest**

None.

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