Etiology of inflammatory bowel disease: A unified hypothesis

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Abstract

Inflammatory bowel disease (IBD), including both ulcerative colitis (UC) and Crohn’s disease (CD), emerged and dramatically increased for about a century. Despite extensive research, its cause remains regarded as unknown. About a decade ago, a series of findings made me suspect that saccharin may be a key causative factor for IBD, through its inhibition on gut bacteria and the resultant impaired inactivation of digestive proteases and over digestion of the mucus layer and gut barrier (the Bacteria-Protease-Mucus-Barrier hypothesis). It explained many puzzles in IBD such as its emergence and temporal changes in last century. Recently I further found evidence suggesting sucralose may be also linked to IBD through a similar mechanism as saccharin and have contributed to the recent worldwide increase of IBD. This new hypothesis suggests that UC and CD are just two symptoms of the same morbidity, rather than two different diseases. They are both caused by a weakening in gut barrier and only differ in that UC is mainly due to increased infiltration of gut bacteria and the resultant recruitment of neutrophils and formation of crypt abscess, while CD is mainly due to increased infiltration of antigens and particles from gut lumen and the resultant recruitment of macrophages and formation of granulomas. It explained the delayed appearance but accelerated increase of CD over UC and many other phenomena. This paper aims to provide a detailed description of a unified hypothesis regarding the etiology of IBD, including the cause and mechanism of IBD, as well as the relationship between UC and CD.

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Key words: Etiology; Inflammatory bowel disease; Ulcerative colitis; Crohn’s disease; Dietary chemicals; Saccharin; Sucralose

INTRODUCTION

As we know, inflammatory bowel disease (IBD) refers to ulcerative colitis (UC) and Crohn’s disease (CD), two highly related debilitating diseases of the digestive tract with similar clinical, pathological, and epidemiological features[1,2]. Although some descriptions in ancient books had been suspected as symptoms of IBD, clustered cases only started to emerge around the end of the 19th century[3]. Right now, IBD has become one of the most common chronic inflammatory conditions only after rheumatoid arthritis, with millions of patients all over the world[3]. It is most prevalent in young adults and remains regarded as incurable, with the patients usually requiring lifelong heavy medication and multiple devastating surgeries like bowel resection, proctocolectomy, ileostomy, and ileal pouch-anal anastomosis, etc[2,4]. As stated by Dr. Kirsner, “ulcerative colitis and Crohn’s disease today represent two of the more challenging diseases in all of medicine”[1].

Since its appearance, people had been puzzled by the constant changes of manifestations of IBD in age, gender, ethnic, temporal and geographical distributions[3,5]. Great efforts have been taken to find out its cause. Many factors had been suspected, including bacteria such as...
Bacillus coli, Bacillus proteus, Bacillus pyocyaneus, Bacillus lactis aerogenes, diplostrepococci, dysentery bacillus, Spherobacter, Spheronubria morphi, Bacillus morganii, Escherichia coli, spirochetes, Mycobacteria (Mycobacteria tuberculosis, Mycobacteria paratuberculosis and Mycobacteria kansaii), Pseudomonas maltophilia, Bacillus vulgatus, Aerobacter aerogenes, Aerobacter esculentus, Aerobacter bifidobacte, Campylobacter fetus ssp. jejuni, Yersinia enterocolitica, and Chlamydia trachomatis, Aeromonas hydrophila, Plesiomonas shigelloides, Edwardsiella tarda, Blistropyxis hominis, Bacteroides vulgatus, Bacteroides fragilis, Pseudomonas maltophilia, Helicobacter hepaticus or pylori species; fungi like Histoplasma and Monilia; virus such as lymphopathia venereum, Bectte's virus, cytomegalovirus, Echo A, B adenovirus, Epstein-Barr, rotavirus, Norwalk virus, influenza, mumps, measles, herpes, Coxsackie A and B, Reovirus, Polio virus, Paramyxovirus; protozoa and parasites like Escherichia histolytica; vaccines such as the trivial maltease, mumps and rubella and Bacillus Calmette-Guérin; microparticles of aluminum, titanium, silicon oxides, calcium phosphate from the diet, tooth paste, dust or soil; drugs like oral contraceptives and non-steroid anti-inflammatory drugs (NSAIDs); dietary components like protein, fat, sugar, fruits and vegetables, margarine, dairy products, coffee, cola, fast food; or glycoalkaloids in potato; smoking; and other factors like refrigeration (cold chain). Despite that, the cause of IBD remains virtually unknown, as none of them can well explain the dynamically changed profiles of IBD. For instance, smoking is currently regarded as the most determined environmental factor for IBD: it reduces the risk of UC, while exacerbates CD. Despite that, the low prevalence of CD in heavily smoking countries like China and high prevalence of CD in the low smoking countries like Canada suggest the contribution of smoking in the general population being negligible and other factors in the environment would have played the predominant role. Another example would be the Mycobacterium avium subspecies paratuberculosis (MAP), a bacteria that causes John’s disease in cattle, that had been suspected the causative factor for CD as early as 1913. Despite a century long research and debate, a causal relationship between MAP and CD still cannot be established. MAP hypothesis also failed to explain the cause of UC, which has been the main form of IBD in most circumstances.

About a decade ago, I found that digestive proteases like trypsin and chymotrypsin can be inactivated by free (unconjugated or deconjugated) bilirubin but not conjugated bilirubin or biliverdin. Further pursuit in the literature led me to suspect that impairment in this process due to inhibition of gut bacteria (thus the major source of β-glucuronidase that is needed for deconjugation of the mostly conjugated biliary bilirubin) by dietary chemicals like saccharin may have played an important causative role in IBD, as the result of damage of the protective mucus layer and the underlying gut tissue by the poorly-inactivated digestive proteases. Recently, I found that sulforaflose, the new generation of artificial sweetener, may exert an even potent impact on gut bacteria than saccharin and have probably contributed to the record high incidence of IBD seen recently in many countries. Based on the evidences gathered and thoughts evolved and developed in the last decade, this paper aims to provide a detailed description of a unified hypothesis regarding the etiology of IBD, including the cause and mechanism of IBD, as well as the relationship between UC and CD.

LARGE COMMERCIAL MARKETING OF SACCHARIN IN 1887 AND THE EMERGENCE OF CLUSTERED CASES OF ULCERATIVE COLITIS SINCE 1888, STARTED FROM THE UNITED KINGDOM

The discovery of saccharin in 1878 from coal tar and its large-scale production and marketing since 1887

Saccharin was discovered in 1878 by Constantin Fahlberg, a young chemist from Germany who engaged in research in Professor Ira Remsen’s laboratory at Johns Hopkins University in Baltimore, Maryland, the United States.

One evening, Fahlberg found extra sweetness of bread and his hand during dinner, and tracked to its source to a coal tar product in the lab. Later, it was revealed that this chemical was 300 to 500 times as sweet as sugar and had little toxicity. In 1882, Constantin Fahlberg himself consumed 10 g of the chemical and experienced no adverse reactions. Most of it passed the body unchanged, through urine or feces. In 1884, associated with his uncle, Adolph List, of Leipzig, Germany, Fahlberg tried pilot experimental production of this chemical in New York and named it as saccharin (also called saccharine at some occasions). Due to the high expenses of labor and materials in New York, Fahlberg, together with his cousin, established the firm Fahlberg, List and Co. and built a factory in Salbke, Germany in 1886 for the commercial production of saccharin. Large quantities of saccharin were produced and reached the market in 1887. After that, more factories were established in Germany. The production of saccharin in Germany before its ban by the end of 1902 is showed in Table 1. Since later 1890’s, factories were also built in other countries like France and the Switzerland. In 1901, John Francis Queeny established Monsanto in St. Louis, Missouri, the United States for the sole purpose of saccharin production. For the first several years, all the saccharin it produced was sold to Coco Cola, then a small company in Atlanta.

The favorite use of saccharin in United Kingdom since 1887 but dislike or ban of saccharin in Germany and most of the other Western countries in the early years

Although saccharin was only produced in Germany in the early years after its marketing in 1887, only about 3% of saccharin was actually consumed in Germany.
mainly due to the bad image of this coal tar product in that country. Saccharin was regarded as being inferior and only consumed by people who could not afford the luxury of sugar[39]. A domestic servants' club even advocated a commitment not to working for people who sweetened their coffee with saccharin instead of sugar[39]. In 1902, saccharin production was eventually brought under strict control in Germany[31]. Only one firm, Fahlberg, List and Co, among the six factories was allowed to continue producing saccharin[9], and it was regulated that saccharin can only be used for medicinal purpose and available through pharmacies[30]. The production of saccharin in Germany reduced from nearly 190 tons in 1901 to about 40 tons in 1903[31], among which only 3 tons were consumed within Germany, with the remaining being exported to other countries[31]. Similar as Germany, many other countries like France, Italy, Spain, Belgium, Holland, Portugal, Russia, Austro-Hungary also put strict regulations on the importation, production, and use of saccharin during these early years[39,40]. These restrictions greatly stimulated the smuggling of saccharin in Europe, with saccharin being hidden in chocolate or match boxes, oil or milk cans, artificial stones or candles, coasts, vests, suits with secret pockets, feed bags for horses, carousel, or even coffins[41].

In contrast to the countries above, saccharin was greatly appreciated in the United Kingdom. Even before its appearance on the market, saccharin had been highly praised by some eminent authorities like Sir Henry E. Roscoe, who had been a member of the parliament, a fellow of royal society, and presidents of Chemical Society, the Society of Chemical Industry, and the British Association[42,43]. In the presidential inaugural address on August 27, 1886, he stated that: "the most remarkable instance is the production of an artificial sweetening agent, termed saccharine, prepared by a complicated series of reactions from coal tar"[42,43]. People were assured by official analysts and doctors that saccharin was harmless and enjoyable[45,46]. Pamphlets with detailed descriptions of many formulae and uses of saccharin were written by professor and editor and distributed to households[45,46]. As stated in a publication in early twenty century: “Here we now have a coal oil product deliberately recommended in England as a valuable and suitable agent for sweetening mineral waters and, presumably, for use wherever it could take the place of genuine sugar. It is altogether different in France, where it has been entirely contraband and even in Germany, where it is manufactured to so considerable an extent, efforts are made to hold it under control[46-48]. Therefore, it would be not surprising that, shortly after its marketing, saccharin soon appeared in almost any family grocer, instead of chemist’s shop in United Kingdom[46]. As the result, United Kingdom was the biggest buyer of saccharin at that time. As stated in the publication: “the American trade (of saccharin) has been inconsequential. In 1891 the export to New York was only about eight hundred kilograms (1800 pounds approximately), while during the same period 7200 kg were shipped to England[49].

**Table 1  Saccharin production in Germany before its ban by the end of 1902**

| Year | Number of factories | Production (tons) |
|------|---------------------|------------------|
| 1888 | 1                   | 5.2[38]          |
| 1889 | 1                   | 14.6[38]         |
| 1896 | 3                   | 33.5[39,40]      |
| 1897 | 4                   | 34.7[39]         |
| 1898 | 5                   | 78.4[41]         |
| 1899 | 6                   | 130.3[42]        |
| 1900 | 6                   | 159.4[42]        |
| 1901 | 6                   | 189.7[42]        |
| 1902 | 6                   | 174.8[42]        |
| 1903 | 1                   | 40[42]           |

**Emergence of clustered cases of ulcerative colitis since 1888, started from United Kingdom**

Although it was suspected that some forms of diarrhea described in ancient books could be sporadic case of UC[1], it appeared that clustered cases of UC only started to emerge after 1888. As stated by Dr. Sidney Philips in his discussion during the first symposium on IBD in the world in 1909 that presented a collection of more than three hundreds of UC patients from 9 hospitals in London: “Ulcerative colitis appeared to be much more common now in this country than formerly. There was no mention of it in any of the published reports of any of the London hospitals before 1888, when Dr. Hale White published cases in Guy’s Hospital Reports. It was not mentioned in St. Bartholomew’s or Westminster Hospital Reports before 1893, nor in the London Hospital Reports till 1897. And the textbooks used twenty or thirty years ago, such as Bristowe’s and Hilton Fagge’s, made no allusion to it. The speaker himself had seen many cases at St. Mary’s Hospital and elsewhere since 1888, but not before then[61]. In addition, Dr. Philips even suspected that the increase in UC might be caused by some food additives. He stated: “Possibly the cause of acute ulcerative colitis was connected with our food supply; tinned or preserved foods might have something to do with it[61]. Interestingly, saccharin was largely used in early years in canned foods to preserve vegetables, fruits and meats, taking the advantage of both its sweet and antiseptic properties[39,42].

**THE WIDESPREAD USE OF SACCHARIN DURING THE TWO WORLD WARS AND THE SPREAD OF ULCEARTIVE COLITIS IN WESTERN COUNTRIES**

During World War I, the shortage of sugar caused great demand for saccharin[33,34]. Figure 1 demonstrated this dramatic increase of saccharin consumption in Germany[35,34]. The ban on saccharin was lifted in Germany and other countries, accompanied by a striking increase in saccharin production[33,34]. In 1916, saccharin production...
in Germany resumed to 1 ton per day\textsuperscript{[58]} . In France, four more factories were equipped to produce saccharin\textsuperscript{[55]}. In the United States, saccharin became allowed using in soft drinks and foods\textsuperscript{[56]}. In addition to increased production, the importation of saccharin in the United States increased from 8 pounds in 1914 to 5617 pounds in 1915 and 12954 pounds in 1916\textsuperscript{[57]} . Despite the increased production and importation, the price of saccharin in New York market increased from $1.15-1.25 per pound in 1914 to $2.85-11.50 in 1915, $11.50-21.50 in 1916, and $20.50-46.00 in 1917\textsuperscript{[53]} , reflected the great increases in the demand and consumption of saccharin during this period.

In accordance with the spread use of saccharin since World War I, UC cases were also more frequently seen in countries other than United Kingdom. As stated by Dr. Evans: “During the recent war (1914-1918), while acting as surgeon to an improvised hospital for Turkish prisoners in Mesopotamia, and later as civil surgeon of Baghdad, an opportunity arose of observing a large number of cases of colitis; the majority were chronic and were complicated by scurvy. The combination of these two diseases made the colitis extremely intractable, and in consequence large numbers died. While in Mesopotamia I performed appendicostomy for intractable ulcerative colitis in ten patients—Turks, Arabs, and Indians\textsuperscript{[59]}. This helped the recognition of UC as an independent entity other than, for instance, dysentery. As stated by Lups S: “In the latter part of the nineteenth century most clinicians considered this affection which later was called ‘ulcerative colitis’ belonging to the dysentery group, even after 1903, when Boas expressed the view that ulcerative colitis was an independent disease. About 1914, however, there was a marked change in the viewpoints of many observers on this question although many still felt that it was of dysenteric origin. They knew full well that only in a few cases true dysenteric organisms were found\textsuperscript{[60]} . In another paper published in 1928, Dr. Thorlakson stated that:“the subject of ulcerative colitis has received a great deal of attention in the medical literature of all countries during the past decade. In reviewing the English, German, French and American literature on this disease, one is struck by the similarity of the articles. It seems obvious that these writers from various countries are all dealing with the same condition, and not, as has been suggested, with different diseases brought under the same name—ulcerative colitis\textsuperscript{[60]} .

In the United States, more cases of UC were seen since World War I. For instance, Logan reported 117 cases of UC treated in Mayo Clinic up to 1918, with 19 cases being before 1915, 18 cases during 1915, 23 cases during 1916, 57 cases during 1917 and to April 1, 1918\textsuperscript{[61]} , while there were 693 cases between 1923-1928\textsuperscript{[62,63]} . In 1922, Dr. Yeomans in the Department of Surgery, Columbia University College of Physicians and Surgeons reported 65 cases of UC mostly observed during 1916 and 1921 with only 6 cases before that\textsuperscript{[64]} . During this period, many UC patients were also reported in California\textsuperscript{[65]}, Massachussets\textsuperscript{[66]}, and other places\textsuperscript{[67]}.

World War II resulted in another jump in saccharin consumption (Figure 1). In the United States, Sigma Chemical Co. was formed to manufacture saccharin and Monsanto resumed large-scale production to meet the high demand\textsuperscript{[68]} . Interestingly, record high incidence of IBD was also seen during this period. For instance, 525 cases of UC were diagnosed in male United States Army in 1944, with a rate as high as 12 per 100 000 in 40-45 age group\textsuperscript{[69]} . This may relate to the preferred use of saccharin in the United States army. As early as in 1896, United States army had chosen saccharin rather sugar as the advantage of its immaterial weight as well as the anti-septic property to reduce the prevalence of diarrheas\textsuperscript{[70]} .
In 1976, approximately 7 million pounds of saccharin was used in foods and beverages designated for special diets or for use in products with reduced calorie content, when low calorie high intensity sweeteners began to be marketed in the United States. This was a huge increase only occurred since late 1950s, with a sharp decline in saccharin consumption in dry food products and syrups, cereals, gums, jams, candies, ice cream and puddings, in addition to as a non-nutritive tabletop sweetener. It was also used in drugs, toothpaste, mouthwashes and cosmetics.

In accordance with this dramatic increase in saccharin consumption, the incidence of IBD also showed a striking increase during this period. This was clearly demonstrated in the study by Stowe et al., which showed the annual incidence of both UC and CD in Monroe County, New York between 1920s and 1986 (Figure 2A). From Figure 2B we can see the increase in IBD for up to later 1970s paralleled nearly with the increased consumption of saccharin during the same period, with a very significant correlation (Figure 2C). The correlation coefficient between saccharin consumption in the United States and the new cases of UC, CD and IBD (UC + CD) in Monroe County were 0.930, 0.935 and 0.948, and the P value being $3.43 \times 10^{-8}$, $1.90 \times 10^{-8}$, and $3.85 \times 10^{-9}$, respectively.

**DISCOVERY OF CARCINOGENICITY OF SACCHARIN IN LABORATORY ANIMALS IN 1970S AND THE LEVELING OFF OR DECREASE OF INFLAMMATORY BOWEL DISEASE OBSERVED IN MANY COUNTRIES SINCE THE SAME PERIOD**

From Figure 2A, we can see the incidence of UC and CD in Monroe County reached a peak in 1978, followed by a mysterious rapid decrease after that. Again, this change was in accordance with the finding of the carcinogenicity of saccharin in animals and the attempt by the Food and Drug Administration (FDA) of the United States to ban its use in the United States in 1977. Due to the protest from the public the congress imposed a two year moratorium instead of a complete ban on saccharin, but passed the Saccharin Study and Labeling Act that required further studies on saccharin and putting a warning label on products containing saccharin. Study showed that these events indeed affected saccharin consumption, especially for those with high education and families with children. Not only in Monroe County in New York, the leveling off or decrease in IBD in later 1970s and 1980s was also seen in other cities of the United States such as Olmsted County, Minnesota, New York and the saccharin consumption in the United States was also seen in other cities of the United States such as Canada, Sweden, and other several countries such as Canada, Sweden, Germany, Japan, Israel, as well as in many other countries such as Denmark, Ireland, and United Kingdom (Figure 3). In 1981 aspartame was approved by Food and Drug Administration (FDA) of the United States for use in dry food products. On July 8, 1983 FDA further approved the use of aspartame in carbonated beverages and syrups. Aspartame soon became the main high intensity sweetener in the market, with a sharp decline in saccharin use and consumption, which was in accordance with the remarkable decrease in the incidence of UC and CD observed in Monroe County at this period (Figure 2A).
THE REBOUNDED USE OF SACCHARIN AND THE INCREASE AGAIN OF INFLAMMATORY BOWEL DISEASE SINCE 1990S

Although a leveling off or decrease in IBD was observed in many places (Figure 3) during the later 1970s and early 1980s, the increase again of IBD since 1990s was observed in many of these places such as Denmark\cite{93}, Sweden\cite{92,94}, United Kingdom\cite{89}, and the United States\cite{76}. This was again in accordance with the rebounded use of saccharin. After finding the carcinogenicity of saccharin in animals in 1970s, many studies were carried out. As the result, most studies failed to show a link between saccharin consumption and bladder cancer in humans\cite{95,96}.

Figure 3  A leveling off or decrease of ulcerative colitis or Crohn’s disease during 1970s and 1980s in the different countries such as Canada, Demark, Germany, Japan, Israel, Sweden, United Kingdom, and United States. UC: Ulcerative colitis; CD: Crohn’s disease.
People gradually regained confidence in saccharin consumption. Saccharin production boomed again, largely because saccharin is very cheap and also very stable thus can be used in a wide range of drink and food products and put on the shelf for a long time[97,98]. In China, saccharin production increased from about 8000 tons in middle 1980s[99], to 13 126 tons in 1991 and 29 175 tons in 1998, accompanied by dramatic increases in both domestic use and exportation[100]. The great adverse impact on sugar industry led the Chinese government adopting strict measures to limit the production and domestic use of saccharin. In the United States, after multiple times of renewal of the two year moratorium, the National Institute of Environmental Health Sciences finally delisted saccharin from carcinogen list in 2000 and the “Sweetest Act” of the Congress eliminated the requirement for putting the warning label on saccharin products[26]. This is accompanied by a dramatic increase in saccharin importation from 2 772 000 pounds in 2000 to 8 346 000 pounds in 2008[101]. In 2007, 52 212 000 pounds of saccharin were exported world wide, with millions of pounds of saccharin being imported in countries like Germany, Spain, United Kingdom, South Korea, Japan, India and Brazil[101]. These massive use of saccharin may have contributed to the worldwide increase of IBD in recent years[102].

SUCRALOSE, A NEW GENERATION OF ARTIFICIAL SWEETENER, MIGHT BE ANOTHER IMPORTANT RISK FACTOR THAT CONTRIBUTED TO THE RECORD HIGH INCIDENCE OF INFLAMMATORY BOWEL DISEASE SEEN RECENTLY IN MULTIPLE COUNTRIES

The evidences demonstrated above provided a simple explanation for many puzzles of IBD such as the emergence and temporal changes of IBD in last century. It suggests saccharin might be the key causative factor for IBD, by primarily its inhibition on gut bacteria[24]. This notion is supported by the recent large-scale studies showing antibiotics greatly increased the risk of IBD[103,104]. Although both saccharin[105-107] and antibiotics can inhibit bacteria, saccharin would have a much more great impact on the general population due to the wide extensive use[108]. When United States FDA attempted a ban on saccharin in 1977, saccharin was used as the only non-nutritive sweetener by up to 70 million Americans[74]. Saccharin was the first and oldest artificial sweetener. From its marketing in 1887 until a temporary decline on sugar industry led the Chinese government adopting strict measures to limit the production and domestic use of saccharin. In the United States, after multiple times of renewal of the two year moratorium, the National Institute of Environmental Health Sciences finally delisted saccharin from carcinogen list in 2000 and the “Sweetest Act” of the Congress eliminated the requirement for putting the warning label on saccharin products[26]. This is accompanied by a dramatic increase in saccharin importation from 2 772 000 pounds in 2000 to 8 346 000 pounds in 2008[101]. In 2007, 52 212 000 pounds of saccharin were exported world wide, with millions of pounds of saccharin being imported in countries like Germany, Spain, United Kingdom, South Korea, Japan, India and Brazil[101]. These massive use of saccharin may have contributed to the worldwide increase of IBD in recent years[102].

THE POSSIBLE MECHANISM OF INFLAMMATORY BOWEL DISEASE: THE BACTERIA-PROTEASE-MUCUS-BARRIER HYPOTHESIS

After the emergence of IBD about a century ago, numerous hypotheses had been suggested as the possible mechanism, which included infection, toxicants, psychogenic disturbances, nutritional deficiencies, allergy to pollens or foods, abdominal trauma, impaired vascular or lymphatic circulation, lysozymes and other enzymes[111,112,113], or the excessive or deficient immune response due to reduced exposure to bacteria or helminthes[114,115]. Many of them were invalidated and forgotten. Up to date, a full coherent mechanistic explanation for IBD is still lacking, but people start to realize that the pathogenesis of IBD involves four fundamental components: the environment, gut microbiota, the immune system and the gene[116,117]. Currently, the dominant theory regarding the increase of IBD involves four fundamental components: the environment, gut microbiota, the immune system and the gene[116,117]. Currently, the dominant theory regarding the increase of IBD involves four fundamental components: the environment, gut microbiota, the immune system and the gene[116,117].
development and response of the immune system due to the reduced exposure to microorganisms such as the microbes in the gut[127,128]. However, this theory neglected another fact: the increased intestinal permeability, which has been observed not only in these patients and their healthy relatives[130,131], but also in their spouse[130,132], suggesting likely a prerequisite condition for these diseases. As the gut contains such a large amounts of bacteria that are ten times of the number of cells of our body and can kill the host thousands of times over, I believe it would be the permeability of the gut rather the absolute number of the bacteria in gut lumen that determined the level of exposure[133]. Therefore, the enhanced immune activities seen in these patients may just be a normal response to the increased infiltration of bacterial and dietary components from the gut lumen[133]. Then the key to the mystery would be to know what caused the increased intestinal permeability in modern society. Here I propose a mechanism for the increased intestinal permeability as well as IBD, featured by the Bacteria-Proteases-Mucus-Barrier hypothesis.

As shown in Figure 5, this hypothesis proposes that the increased intake of dietary chemicals like saccharin and sucralose caused a significant reduction in gut bacteria, along with a failure for prompt replenishment due to the improved hygiene in modern society. This led to a remarkable decrease in β-glucuronidase in gut lumen, resulting in impaired deconjugation of the biliary bilirubin and the subsequent inactivation of digestive proteases. Then these poorly inactivated proteases work synergistically with the glycosides from the remaining bacteria to cause an accelerated degradation of the mucus layer, resulting in damage of the gut barrier (the Bacteria-Protease-Mucus-Barrier hypothesis). This will further result in infiltration of bacteria and their components (mainly in the large intestine) and recruitment of neutrophils.

Qin X. Etiology of IBD

Figure 4 Relationship between the increase of inflammatory bowel disease and approval of sucralose in countries like Canada, Australia, United States and Norway. IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn’s disease.
Figure 5 An overall hypotheses for the cause and mechanism of inflammatory bowel disease (both Crohn’s disease and ulcerative colitis).

leading to the formation of crypt abscess\textsuperscript{[26]}\textsuperscript{[26]}, the characteristic change of UC\textsuperscript{[134]}; while at places or situations being relative sterile, the increased infiltration of antigens and particles from the gut would result in accumulation of macrophages and formation of inflammatory granuloma\textsuperscript{[26]}, the hallmark of CD\textsuperscript{[134]} (Figure 5). This would further induce enhanced immune response of the body, leading to further damage of the gut as well as extra-intestinal manifestations in the joints, skin, eyes and mouth, etc\textsuperscript{[135,136]}. More detailed descriptions regarding the proposed mechanism can be found in the corresponding references\textsuperscript{[20,21,108,133,136-151]}.

**ULCERATIVE COLITIS AND CROHN’S DISEASE ARE LIKELY JUST TWO SYMPTOMS OF THE SAME MORBIDITY RATHER THAN TWO DIFFERENT DISEASES**

The Bacteria-Protease-Mucus-Barrier hypothesis and mechanism of IBD as described above and illustrated in Figure 5 suggest that UC and CD share virtually the same cause, thus UC and CD would be just two symptoms of the same morbidity rather than two different diseases. This notion contradicts the current main stream of thoughts that are trying to dissect UC and CD into multiple subtypes with different causes and diverse mechanisms\textsuperscript{[152]}. Nevertheless, this new perception is in accordance with many facts. Figure 6 further illustrated the mechanism of IBD as well as the relationship between UC and CD. It explained why gut damage and IBD started to appear and became more prevalent along with the improved sanitary condition but failed to develop under both conventional and germ-free condition\textsuperscript{[144]}, and predicted a shift of predominance from the bacteria-mediated UC to antigen/particle-mediated CD along with the decrease in gut bacteria in modern society or other circumstances (Figure 6B). It provided a simple explanation for many big puzzles in IBD such as: (1) the discrepancy between the temporal changes of UC vs CD: Many studies had revealed a regular pattern that UC emerged first, then reached a plateau or even started to decrease, while CD showed a delayed appearance but accelerated increase with an eventual tendency to pass UC\textsuperscript{[20]}; (2) the increase in colonic CD over time: Studies in Stockholm County, Sweden found that colonic CD increased from 15% during 1959-1964 to 32% during 1980-1989, and further to 52% during 1990-2001, while the ileocaecal CD decreased from 58% during 1959-1964 to 41% during 1980-1989, and to 28% during 1990-2001\textsuperscript{[146,147]}. Similar changes were also observed in other long-term studies such as the one conducted in Cardiff, United Kingdom\textsuperscript{[148]}. Again, Figure 6B illustrated the anticipated shift of UC to colonic CD over time; (3) the inverse relationship between age and colonic CD in children: It is found that the younger the children, the more likely they had colonic CD\textsuperscript{[89]}.
CONCLUSION

Currently, tremendous efforts have been taking for research on the genes, the microbiota and the immune system: genome-wide association studies to find out the susceptible loci among the tens of thousands of genes in our body; metagenome, metaproteome, and metabolome analyses of gut microbiota that contains more than 100 times of genes than our own genome\(^{159}\) to find out the bacteria responsible; and extensive studies on the many cells, signal pathways, mediators and cytokines of the immune system to find out aberrant immune response.\(^{127,128,156-158}\) IBD emerged and became epidemic for about a century, suggesting the factors in environment rather than the gene or other factors within the body would be the primary cause. Increased risk of IBD in twins, families, or the same ethnic groups may attribute to not only the gene, but also environmental factors they shared such as the type of diet\(^{159,160}\). This article proposes saccharin being the key causative factor that contributed greatly to the emergence and epidemic of IBD in last century. As described above, there were big variations in saccharin regulation and consumption among the different countries and also in the different periods or even different parts (such as the different states in the United States\(^{161}\)). Within a country. This may explain the constant temporal changes and big geographical variations in IBD, and why similar changes were more likely seen within the border of a country rather than the closeness between cities\(^{155}\). In the developed countries, saccharin may be more frequently used by white collars working in the office, while saccharin may be more likely consumed by people in lower class in the developing countries due to its cheapness. This may contributed to the high incidence of IBD in high social, economical, educational status in the developed countries\(^{162}\), while some early study in India found almost all the patients belonged to the middle and poorer classes under poor hygiene condition\(^{163}\), in accordance with a heavy saccharin consumption in that country\(^{164}\). This would suggest improved hygiene itself might facilitate but still not be sufficient, while some dietary chemicals might be enough to cause significant impact on gut bacteria and IBD. This notion is also in accordance with the close relationship of IBD with westernization rather industrialization, as demonstrated by the much low incidence of IBD in the developed countries like Japan, Singapore and Hong Kong\(^{158,160}\). The recent increase again of IBD in the developed countries is also unlikely attribute to a further improvement in hygiene condition. At early times, saccharin was mainly used as a tabletop sweetener in the restaurants, tea houses or coffee shops, thus men may have more chance to consume than housewives. However, in modern society, dietary drinks or foods may be more consumed by young ladies for concerns on their body weight. This may account for the

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Figure 6: Ulcerative colitis and Crohn’s disease are likely just two symptoms of the same morbidity rather than two different diseases. A: The structure of mucin; B: Mechanistic sketch of the temporal changes of ulcerative colitis (UC) and Crohn’s disease (CD) and their relationship. A reduction in gut bacteria along with the improved hygiene and increased intake of dietary chemicals like saccharin and sucralose will result in impairment in digestive proteases inactivation. The poorly inactivated proteases will work together with glycosidases from the gut bacteria to cause accelerated degradation of the mucus layer that is proposed here paralleling the risk of developing inflammatory bowel disease (IBD = UC + CD). UC and CD differ in that UC is caused by the increased infiltration of bacteria and the resultant recruitment of neutrophils and formation of crypt abscesses, while CD is caused by increased infiltration of luminal antigens and particles and the resultant recruitment of macrophages and formation of granulomas. Thus the reduction in gut bacteria along with the modernization or other factors will result in a shift of predominance from the bacteria-meditated UC to antigen/particle-mediated CD. Max: Maximum.

with genes related to neutrophil extravasation and epithelial defense such as LSP1\(^{158}\).
changes and variations in gender and age of IBD over time. The recent finding of the even stronger impact of sucralose on gut bacteria further provided a possible explanation for the record high IBD observed recently in multiple countries, as well as the remarkable increase of IBD in children. Epidemiological study revealed spotted areas with high IBD. Probably we should add another thing to the checklist: to see if there is any famous bakery, restaurant, or bar where foods or drinks are sweetened heavily by these artificial sweeteners.

Although it is proposed here that saccharin and sucralose might be the key causative factors for IBD, it does not mean to rule out that some other genetic or environmental factors may also be capable of affecting or contributing to IBD one way or the other.

However, the peculiar changes of IBD such as the recent worldwide increase of IBD, especially in the developed countries in children, seems unlikely to be explained by any of the currently suspected factors like the genes, smoking, NSAIDs, concepative, appendectomy, sunshine and vitamin D, refrigeration, reduced exposure to bacteria, virus or worms, etc. Therefore, a fundamental breaking through in IBD would largely depend on finding out the key causative factors in the environment and thus the root mechanism of IBD. This paper proposed that impaired inactivation of digestive proteases due to the inhibition of gut bacteria by dietary chemicals like saccharin and sucralose being the primary mechanism. This would suggest it is not any pathogen but the digestive proteases produced by our body to digest the food for survival being the principal culprit for IBD. Under conventional conditions, the commensal bacteria (the microbiota) would be a valuable partner of our body by helping promptly inactivating these destructive proteases, probably by simply providing their enriched β-glucuronidase needed for deconjugation of biliary bilirubin. Thus the gut microbiota should be treated as an “microbial organ” of the body and taken into consideration when assessing the toxicity of chemicals or the adverse effects and efficacy of drugs. However, the microbiota could be beneficial and also could be detrimental. Once there were not enough gut bacteria to help maintaining the function of gut barrier, they would start to leak into the body and become the driving force for the chronic inflammation seen in IBD. Once getting into the body, none of the commensal bacteria will remain our friend and our body will fight desperately against it. It seems unlikely and might also be unnecessary to pin down to one or a couples strains of bacteria exclusively responsible for IBD by screening the tens of thousands of species of bacteria in gut microbiota. The enhanced immune activity in IBD would be just the normal reaction to the infiltrated bacterial and dietary components from gut lumen rather than an unbalanced or aberrant immune response, which may explain the remarkable increase of both the Th1-mediated CD and Th2-mediated UC in modern society. It is proposed here that UC and CD are just two symptoms of the same morbidity rather than two different diseases. Some recent studies revealed that colonic CD had become the main form of CD. Apparently, the CD we are talking about today is no more the “regional ileitis” when this disease was defined by Crohn et al. in 1932. These CD cases are also no more the resemblance of Johne’s disease in cattle, but rather IBD frequently seen in dogs and cats. Many of the colonic CD diagnosed today would be just UC cases early. On the other hand, the advance in endoscopies and other technologies led to reveal that a substantial portion of UC patients have ileitis (backwash ileitis) and the prevalence of inflammation seen in the esophagus, stomach, and duodenum is comparable among CD and UC, further suggesting the intimate similarities between UC and CD. As stated above, the discrepancy between the temporal changes of UC vs CD would actually reflect their intimate connection. Elucidating the true relationship between UC and CD would be the crucial step for a full understanding of IBD.

This paper proposed a unified hypothesis regarding the etiology for IBD, including the cause and mechanism of IBD as well as the relationship between UC and CD. It provides a simple explanation for many puzzles of IBD. However, just like all other hypothesis and even existing theories well written in textbooks, it must be tested against facts. In the last decade, I have contacted multiple national and international organizations and IBD professionals suggesting checking out the possible link between saccharin and IBD, but failed to raise any action. I have also tried multiple times to apply grants from different agents, but remain unsuccessful. Hope this article may draw more attention and efforts. IBD just emerged and became epidemic for about a century and would be preventable and also likely curable, but first we may need to find out the key causative factors and thus the primary and fundamental mechanism.

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