The biocultural evolution of inflammatory bowel diseases

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Abstract
Inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, are described as abnormal immune responses to the gastrointestinal microbiota. The etiology of IBD is unknown; however, it is associated with Western, industrialized societies. A better understanding of the origins and treatments of IBD can lead to improved health outcomes. This paper seeks to examine IBD from a cultural, environmental, and evolutionary perspective. The effects of cultural and environmental factors, such as diagnostic practices, diet, breastfeeding practices, antibiotic use, appendectomy, and environmental radiation exposure on the risk of developing IBD are discussed. The efficacy of various treatments for IBD will also be examined. This review suggests that IBD constitutes a maladaptive inflammatory response to microbial ecosystem changes in the gut brought about by a variety of external factors, including diet, breastfeeding, appendectomy, antibiotic usage, and environmental radiation exposure.

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Table of Contents

Acknowledgments........................................................................................................................... 3
Abstract........................................................................................................................................... 4
Introduction.................................................................................................................................... 5
Evolutionary Medicine and IBD ....................................................................................................... 6
Diagnostic Practices ....................................................................................................................... 9
Immune Response in IBD ................................................................................................................ 11
Cultural and Environmental Factors that Impact IBD Risk ............................................................ 13
  Diet ......................................................................................................................................... 13
  Breastfeeding ........................................................................................................................ 19
  Appendectomy ...................................................................................................................... 21
  Antibiotics ............................................................................................................................. 23
Environmental Radiation ............................................................................................................. 26
Treatments for IBD ......................................................................................................................... 28
  Alterations to the Microbiome (Probiotics and Fecal Microbiota Transplants) .......................... 29
  Complementary and Alternative Medicine .............................................................................. 31
Discussion ...................................................................................................................................... 34
References Cited ............................................................................................................................. 39
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Abstract

Inflammatory bowel diseases (IBD), such as Crohn’s disease and ulcerative colitis, are described as abnormal immune responses to the gastrointestinal microbiota. The etiology of IBD is unknown; however, it is associated with Western, industrialized societies. A better understanding of the origins and treatments of IBD can lead to improved health outcomes. This paper seeks to examine IBD from a cultural, environmental, and evolutionary perspective. The effects of cultural and environmental factors, such as diagnostic practices, diet, breastfeeding practices, antibiotic use, appendectomy, and environmental radiation exposure on the risk of developing IBD are discussed. The efficacy of various treatments for IBD will also be examined. This review suggests that IBD constitutes a maladaptive inflammatory response to microbial ecosystem changes in the gut brought about by a variety of external factors, including diet, breastfeeding, appendectomy, antibiotic usage, and environmental radiation exposure.
Introduction

Inflammatory bowel diseases (IBD) such as Crohn’s disease (CD) and ulcerative colitis (UC) are often characterized by an “abnormal immune response to the intestinal microflora of a genetically susceptible individual” (Ananthakrishnan, 2015). Although the etiology of IBD has been studied extensively, the root cause of the disease is yet to be understood. In addition, research on the pathogenesis of IBD is becoming of increasing importance, as epidemiological studies suggest that IBD is quickly becoming a global disease (Molodecky et al., 2012). Through understanding how various factors influence the pathogenesis of IBD, better prevention strategies and treatment plans can be developed. This will ultimately lead to improved patient health outcomes.

It is currently unknown if the recent increase in IBD incidence and prevalence rates are due to genetic or environmental factors. Although there is some genetic basis for IBD, monozygous twin studies have suggested that only a 50-60% concordance rate exists, meaning that genetics can only be partially responsible for the pathogenesis of IBD (Halfvarson et al., 2003; Orholm et al., 2000). Furthermore, migrant population studies suggest that racial and ethnic differences in incidence rates of IBD are due to cultural and environmental differences rather than actual genetic differences (Loftus, 2004). Thus, environmental and cultural influences must play a significant role in the pathogenesis of IBD, and further research should be conducted in order to understand the relationship between these factors and the etiology of the disease. Increased risk of IBD has also been linked to a dysregulated immune response to the intestinal microbiome (Kostic et al., 2014), and both bacterial and fungal dysbiosis has been observed in the gut of IBD patients, suggesting that the bacterial and fungal microbiome may play a role in
IBD pathogenesis (Sokol et al., 2017). Thus, the relationships between these cultural factors, intestinal microbiota, and the immune response should be studied.

Despite the copious amounts of research on environmental risk factors for IBD, few studies have examined these environmental factors from a cross-cultural perspective. Through analyzing these cultural differences and their biological impact, a clearer understanding of the etiology of IBD may begin to arise. Of particular interest will be those changes in cultural practices that are associated with the industrialization of nations, as industrialization is often linked to an increase in risk of IBD (Ananthakrishnan, 2015).

The goal of this literature review will be to: 1) examine the effect that diagnostic practices have on IBD incidence and prevalence rates, 2) analyze the biological impact that cultural and environmental factors such as diet, breastfeeding practices, antibiotic use, appendectomy, and environmental radiation exposure have on the intestinal microbiome and the immune response, and 3) evaluate the efficacy of common IBD treatments. It is hypothesized that IBD is caused by a maladaptive immune response to a gastrointestinal environment that has experienced rapid changes due to industrialization. Thus, those treatments that restore the gastrointestinal environment to a “healthy” state should be most beneficial for patients with IBD.

**Evolutionary Medicine and IBD**

Current evolutionary theory (termed the “modern synthesis”), pioneered by Mayr and Dobzhansky and coined by Huxley, combines genetics and Darwinian evolution (Kutschera and Niklas, 2004). The Darwinian theory of evolution by natural selection has
four basic principles: 1) in each generation, more organisms are produced than can survive; 2) organisms exhibit variability of traits; 3) some of this variation is heritable; and 4) those individuals who are better suited for their environments are more likely to survive and pass down favorable traits. Scientists have revised Darwin's understanding of evolution to include Mendelian genetics. The four tenets of this "modern synthesis of evolution" are 1) changes in DNA create changes in the phenotype (observable characteristics) on which natural selection acts; 2) the phenotypes best suited for the environment are more likely to survive and reproduce; 3) those phenotypes that survive will pass on more genes to the next generation; and 4) a change in gene frequency from one generation to the next is evolution. Through this evolutionary framework, scientists are able to better understand biological diversity and human variation (Huss-Ashmore, 2000).

According to Darwinian evolution, the environment is the primary driving force of natural selection. For humans, the environment has been suggested to contain three aspects: the physical (climate, energy usage, materials, and geology), the biotic (food, materials, pathogens, symbionts, and predators), and the social (social, economic, and political structures, material culture, technology, and population dynamics) (Huss-Ashmore, 2000). In all these environments, humans face two challenges: they must avoid stressors (conditions that may disturb normal biological processes) and find resources for survival and reproduction (Huss-Ashmore, 2000).

In order to overcome these challenges, humans employ a combination of genetic, physiological, developmental, cultural and behavioral responses. In addition, although cultural and behavioral responses attempt to alleviate environmental stressors, they may
also be the source of environmental stressors for certain sections of the population. For example, children living in poverty-stricken urban environments are exposed to higher lead levels than the rest of the population, which can lead to a number of negative biological outcomes (Huss-Ashmore, 2000). This was the case in the 2014 Flint water crisis, which had a disparate impact on low-income and minority children and pregnant women. Intending to save money, state-appointed emergency management chose to switch the water source from Detroit's Lake Huron to the Flint River. This change significantly increased lead exposure in low socioeconomic areas within the city limits, whereas neighborhoods outside the city were not significantly affected (Hanna-Attisha et al., 2016). Therefore, the environment both affects and is affected by human biobehavioral responses. Furthermore, analyzing the context in which these responses are created is important for understanding their success. Responses that are successful in one context may not be successful in another, and responses that are successful now may not be successful in the future (Goodman and Leatherman, 2010).

The theory of evolution can also be applied to biomedical contexts. In the field of evolutionary medicine, human health and illness are understood through analyzing human evolutionary history. In particular, evolutionary medicine focuses on how evolutionary trade-offs (traits that are advantageous, but come at a cost) and different environments impact human health (Huss-Ashmore, 2000). This perspective is thought to be especially useful for understanding chronic illnesses, like IBD, because it attempts to understand the ultimate causes of these diseases. In other words, evolutionary medicine examines how changing environments and lifestyle differences between modern and ancient humans contribute to modern human health (Trevathan et al., 2008).
Environmental factors are thought to play a major role in IBD pathogenesis (Loftus, 2004). Furthermore, the gut microbiome, which is altered in IBD patients (Kostic et al., 2014; Swidsinski et al., 2002; Swidsinski et al., 2005), is more affected by environmental factors than by host genetics. For example, cohabitating but genetically unrelated spouses have gut microbiomes that more closely resemble each other than individuals from separate households (Yatsunenko et al., 2012). In addition, dogs (Canis lupus familiaris) have intestinal microbiomes that are more similar to humans than pigs or mice. This similarity is most likely due to the fact that humans and dogs live in similar environments (Coelho et al., 2018). Thus, it is likely that cultural and behavioral responses to environmental stressors may impact the gut microenvironment. These changes to the gut microenvironment create a new context in which certain adaptations may be unsuccessful, ultimately leading to chronic digestive diseases such as IBD.

Diagnostic Practices

Better access to healthcare and advances in diagnostic procedures and medical technology are thought to be important contributing factors for the increased prevalence and incidence rates of IBD (Kaplan, 2015; Lakatos, 2006; Loftus, 2004; Molodecky et al., 2012). In particular, understanding diagnostic changes may help to explain why newly-industrialized nations experienced an initial increase in rates of UC, followed by an increase in rates of CD years later (Kaplan, 2015; Lakatos, 2006; Loftus, 2004). In newly industrialized nations, UC is diagnosed by sigmoidoscopy (which examines only the rectum and distal colon), but CD diagnosis is rare and is limited to severe cases, such as those that require surgery. However, as colonoscopy screening increases (which
examines the entire large intestine and the distal small intestine), milder cases of CD are more easily detected. Thus, changes in diagnostic practices are responsible for the initial rise in UC, followed by a rise in CD (Kaplan, 2015). Therefore, understanding how IBD is diagnosed worldwide is important for understanding the epidemiology of the disease.

In the United States, it is recommended that a patient presenting symptoms of IBD have an initial evaluation conducted that includes a colonoscopy with intubation and examination of the terminal ileum (the most distal portion of the small intestine). This allows for direct visualization of the colon and terminal ileum and for the performance of any necessary biopsies. Sigmoidoscopy is not suggested for initial evaluation, but may be used for monitoring patients with established IBD (Spiceland and Lodhia, 2018).

In non-Western societies, diagnostic challenges may arise from overlapping symptoms of IBD and infectious diseases such as intestinal tuberculosis, which mimics IBD and lacks strong diagnostic histopathological criteria. For example, access to healthcare can vary between urban and rural populations and by location (Baumgart et al., 2011). Therefore, it is likely that as access to healthcare and diagnostic technology improve, there will be an increase the reporting of IBD to health agencies, which will impact the incidence rates of IBD.

A study conducted by Pavlovic-Calic and colleagues (2008) found that increasing rates of CD in Tuzla Canton of Bosnia and Herzegovina was directly correlated to increased availability of colonoscopy. Between 1995 and 1997, the incidence of CD was about 0.3 per 100,000. By 2006, the incidence of CD had jumped to nearly 5.0 per 100,000. This dramatic increase in incidence was determined to be due to an increase the availability of endoscopy. As a result of the Bosnian War (1992-1995), health-care
infrastructure and access to endoscopy had been crippled, and only 29 endoscopies were performed in 1995. By 2006, conditions had improved, and gastroenterologists reportedly performed 850 endoscopies (Pavlovic-Calic et al., 2008). This study serves as evidence that increased incidence of IBD may be due to increased use of colonoscopy.

Better access to healthcare and improved diagnostic techniques are not the only factors that can affect incidence rates of IBD. In addition to an increase in colonoscopy usage, the spread of “Western” lifestyle and diet following the civil war were suggested as possible compounding factors (Pavlovic-Calic et al., 2008). In industrialized nations, for unknown reasons, the incidence of pediatric-onset IBD has been on the rise (Kaplan, 2015). Thus, although changes in diagnostic practices are a major reason for increased rates of IBD, they are not the only reason. Although these changes may lead to better diagnoses, they do not necessarily help to explain the etiology of IBD. Therefore, an examination of other factors known to impact gastrointestinal health is required.

**Immune Response in IBD**

IBD is characterized as an aberrant immune response to the gut microbiota in a genetically susceptible individual (Ananthakrishnan, 2015). In IBD, the immune response is regulated by both the innate and the adaptive immune system. The innate immune system is often the first line of defense against pathogens. In the gut, the innate immune system includes the epithelial barrier and phagocytic cells (immune cells that engulf pathogens, and includes macrophages, dendritic cells, and neutrophils). Although the innate immune system has no memory for pathogens (Mayer, 2010), it is what normally protects the gut against harmful bacteria, since the adaptive immune system can take days
to respond (Weinstock and Elliott, 2009). The majority of genes that have been discovered to play a role in IBD pathogenesis disrupt the innate immunity of the gut. Although a mutation in one of these genes is not essential for disease development, those with a mutation and IBD have earlier disease onset and more aggressive disease characteristics (Mayer, 2010).

The adaptive immune system has also been found to be involved in the progression of IBD. This system is mediated by lymphocytes, T cells, B cells, and antigen receptors. Of these immune cells, T cells are the most correlated with IBD pathogenesis. T cells are responsible for producing cytokines (cell-signaling molecules) that affect other immune cells (Mayer, 2010). Unlike innate immunity, the adaptive immune system responds to specific pathogens and can have memory of them. From an evolutionary perspective, it has been hypothesized that the regulation of cytokine production by certain gut symbionts may have played a role in the evolution of the human immune system. In particular, helminths (parasitic worms) are believed to aid in the regulation of cytokine production. Therefore, exposure to helminths throughout human evolution may have affected the evolution of the immune system, and may continue to regulate immunological processes today. According to the “hygiene hypothesis,” children raised in hygienic environments are not exposed to certain pathogens and parasites, like helminths, and thus are more susceptible to immune disorders, such as IBD (Weinstock and Elliott, 2009).

Due to the fact that it must be able to respond to a variety of pathogens and changing environments, the immune system is plastic by nature (Mayer, 2010). However, as the hygiene hypothesis suggests, it is important to remember that the immune system
has evolved alongside a specific gut environment (Weinstock and Elliott, 2009). Therefore, as the intestinal microenvironment changes in response to external factors, it is possible that immune responses that have adapted to certain environments are no longer successful in these new environmental contexts. It is therefore essential to examine the ways that external factors impact the intestinal ecosystem.

Cultural and Environmental Factors that Impact IBD Risk

Diet

Epidemiological studies on IBD have often found a correlation between industrialization and an increased risk of IBD (Molodecky et al., 2012). It has been suggested that urbanization and increased wealth is associated with diets higher in sugar, animal fats and proteins, and processed foods (Drewnowski and Popkin, 1997). Furthermore, most IBD patients believe that diet plays a major role in the development of the disease. Thus, it seems that cultural differences in diet have a large impact on the pathogenesis and risk of IBD. Although it has been one of the most extensively studied risk factors, it is also one of the most difficult to research due to the high variation in individual diet patterns (Ananthakrishnan, 2015). By studying these dietary factors from a cross-cultural, evolutionary perspective, trends in intestinal microbiology, diet, and possible etiologies of IBD begin to emerge.

Numerous studies have suggested that the intestinal microbiome of IBD patients differs greatly from that of healthy individuals (Kostic et al., 2014; Sunkara et al., 2018; Swidsinski et al., 2002; Swidsinski et al., 2005). For example, patients with IBD have been found to have higher amounts of Bacteroides and Enterobacteriaceae, including E.
coli, than healthy controls (Swidsinski et al., 2002). In fact, Bacteroides adhesion to the intestinal mucosal layer is considered a main feature of the intestinal microbiome in patients with IBD when compared to healthy individuals (Swidsinski et al., 2005). Dysbiosis of the fungal microbiome has also been observed in IBD patients. In particular, the gut microenvironment of CD patients may favor fungi at the expense of bacteria, suggesting there are inter-kingdom microbial shifts occurring in the GI tract of IBD patients (Sokol et al., 2017).

In addition to a link between the gut microbiome and IBD, it has been suggested that shifts in dietary patterns may also shape the taxonomic structure of the intestinal microbiome, at least temporarily. When fed a Western diet, African green monkeys (Chlorocebus aethiops sabaeus) have intestinal microbiomes with increased microbial richness and relative abundance of Prevotella (Amato et al., 2015b). In humans, however, a shift to a Western diet high in animal fats and proteins has the opposite effect on microbial taxa, most likely due to dietary and physiological changes that occurred during human evolution. One US study on healthy individuals found that agrarian, carbohydrate-rich diets were associated with a gut microbiome with high amounts of bacteria belonging to the Prevotella taxa. In contrast, diets high in animal fats and proteins were associated with an intestinal microbiome high in Bacteroides (which are associated with IBD when present in high levels) (Wu et al., 2011). Given that higher amounts of Bacteroides are observed in IBD patients (Swidsinski et al., 2002; Swidsinski et al., 2005), there may be a link in humans between a diet high in animal fats and proteins and IBD risk.
It has been suggested that differences in response to changes in diet between humans and non-human primates may be due to dietary and physiological shifts in human evolution that have affected the microbiota. Changes in this microbiota may have also led to more efficient energy production and fat storage. Although this potentially increased brain size and reduced gut size, it additionally may have made humans more susceptible to obesity and metabolic disorders in times when food resources are abundant (Amato et al., 2015b). As obesity has been linked to increased inflammation (Celiberto et al., 2018), it is possible that increased susceptibility to obesity may also increase susceptibility to chronic inflammatory disorders, such as IBD.

Significant differences in the composition of the microbiota of agrarian and industrial societies have also been observed. A study comparing the intestinal microflora of children in Burkina Faso, where IBD is a rare occurrence, to that of children of Italy, where IBD is relatively common, found that the microflora of the populations differs significantly. Although it is unknown why IBD prevalence rates differ between populations, researchers hypothesized that this was due to environmental factors. The diet of children of Burkina Faso is thought to resemble that of early agrarian societies, and is composed of cereals, such as millet and sorghum, legumes, vegetables, and a small amount of animal protein from chicken and termites. These children had gut microbiomes rich in *Prevotella*, *Xylanibacter*, *Butyrivibrio*, and *Treponema* (bacterial genera are known to produce short-chain fatty acids, which are thought to protect against intestinal inflammation). In contrast, children in Italy ate diets high in animal proteins, sugars, and fats, and low in fiber (De Filippo et al., 2010). This diet is common amongst Western societies and has been associated with an increased risk of IBD (Albenberg and Wu, 2015).
The intestinal microbiome of Italian children showed almost no *Prevotella* bacteria and higher amounts of *Bacteroides* when compared to children of Burkina Faso. In addition, the Italian children had significantly higher percentages of *Enterobacteriaceae*, including *Shigella* and *E. coli* (bacterial pathogens known to cause diarrhea), which were mostly absent in the intestines of children from Burkina Faso (De Filippo et al., 2010). A similar inverse relationship between *Prevotella* and *Bacteroides* has been seen in studies comparing the intestinal microflora of individuals from South America and Bangladesh to those from more industrialized nations (Albenberg and Wu, 2014).

Aside from comparing the intestinal microbiota of agrarian societies to that of industrialized nations, research has also been conducted on the intestinal microbial makeup of hunter-gatherer societies. One study on the Hadza hunter-gatherers of Tanzania found significant differences in the intestinal microbiome of these populations when compared to Italian populations. Similar to the population studied in Burkina Faso, the majority (about 70%) of the energy needs of the Hadza came from plant food. As a result, the gut microbiome of the hunter-gatherers in Tanzania consisted of features that were consistent with a heavily plant-based diet. Like the Burkina Faso populations, the intestinal microbiome of the Hadza included a higher percentage of *Prevotella* and a lower abundance *Bacteroides* when compared to the Italian population. In addition, Hadza populations exhibited increased biodiversity of the intestinal microbiome compared to the Italian populations (Schnorr et al., 2014). A decrease in biodiversity due to the loss of ancestral microbial species has been hypothesized to be linked to an
increase in allergic and metabolic diseases (Blaser and Falkow, 2009). Therefore, a decrease in diversity may also be linked to autoimmune disease such as IBD.

Interestingly, the intestinal microbiome of Hadza hunter-gatherers undergoes cyclical changes in response to seasonal variation in dietary habits. During the wet season (November through April), berry foraging and honey consumption is more successful. However, during the dry season (May through October), the Hadza engage more frequently in hunting strategies for subsistence. During these seasonal cycles, the abundance of many taxa falls below the detectable range only to reappear in the next season. These taxa that disappear in the Hadza at certain points of the year are also taxa that are rare or absent in industrialized populations, such as those microorganisms belonging to the Spirochaetaceae and the Succinivibrionaceae family (Smits et al., 2017). The gut microbiota of wild black howler monkeys has also been observed to undergo seasonal variation in bacterial taxa. It is hypothesized that this ability of the microbiome to shift in response to dietary variation may have an adaptive function, as changes in microbial taxa may help the host meet nutritional demands during times of resource limitation resulting from seasonal variation (Amato et al., 2015a).

In addition to cross-cultural studies on human diet and the intestinal microbiome, studies on the biological implications of the changes in gut microbiota are essential to understanding the relationship between these changes and IBD. It has been suggested that human intestinal bacteria have coevolved with changes in diet (Ley et al., 2008). In both the Burkina Faso and Hadza populations, it is hypothesized that the microbiota coevolved with diet in order to maximize energy intake from indigestible carbohydrate compounds (De Filippo et al., 2010; Schnorr et al., 2014). This evolution in gut microflora took the
form of increased amounts of *Prevotella*, *Xyanibacter*, and *Treponema*. Coincidently, these taxa are mostly absent from the European children studied. In addition to fulfilling the need to maximize energy intake from plant foods high in indigestible fiber, these bacteria also produce short-chain fatty acids, which have been shown to protect against intestinal inflammation. The high number *Bacteroides* observed in the European children also help to produce short-chain fatty acids, suggesting an evolutionary need for their production. However, the production level of these short-chain fatty acids was still less than in the children of Burkina Faso (De Filippo et al., 2010).

Based on the above studies, it is likely that dietary changes that occur with industrialization are a leading factor in the increased risk of IBD. The relationship between these changes and IBD risk is most easily seen in Asia, where IBD was rarely observed up until the last few decades (Lakatos, 2006). In Japan in particular, the number of patients with IBD has increased 100-fold within the last 30 years. Since World War II, Japan has faced enormous cultural changes, including a shift to a more Westernized diet. Prior to WWII, a typical Japanese diet consisted of mostly vegetarian meals comprised of rice and barley, miso soup with root vegetables and/or tofu, fermented pickles, and a small amount of animal protein from fermented fish. However, within the last few decades, the Japanese diet has begun to include more foods associated with Western diets. This includes higher amounts of sugars, fats, and animal proteins and a decrease in the amount of dietary fiber (Kanai et al., 2014). It is likely that these dietary changes are among the many factors that led to the 100-fold increase in IBD patients in Japan in the last 30 years, and are likely impacting the worldwide incidence and prevalence rates as well.
Breastfeeding

Aside from cultural shifts in adult diets, changes in infant feeding practices may also lead to an increased risk of IBD. The first studies on the link between breastfeeding and IBD began in the 1960s when researchers discovered that patients with UC were more likely to never have been breastfed (Mikhailov and Furner, 2009). Since then, numerous studies have been conducted in order to find a link between breastfeeding and the risk of IBD. However, many of these studies are either conducted with small sample sizes or they fail to find any correlation between infant feeding practices and IBD risk (Klement et al., 2004). Nonetheless, breastmilk has been associated with several health benefits, such as protection against infectious diseases, asthma, allergies, and type 1 diabetes mellitus (Klement et al., 2004; Rinne et al., 2005), and may still play an important role in the etiology of IBD.

Of these various health benefits, breastfeeding may reduce the risk of IBD by selectively promoting the growth of intestinal bacteria that protect against pathogens and immune-related diseases (Klement et al., 2004). Human milk oligosaccharides (MOS), the third largest component of human milk, are indigestible by the human digestive tract and remain intact as they travel through the colon. However, MOS are important prebiotics that nourish the growth of certain intestinal bacterial species, specifically *Bifidobacteria*. *Bifidobacteria* are thought to strengthen the intestinal mucosal barrier by increasing the production of immunoglobulin A (an antibody that plays a role in the immune function of mucosal membranes) (Albenberg and Wu, 2014). Immunoglobulin A is believed to enable secretion of antibodies on mucosal surfaces, which protect against dietary antigens and toxins and prevent the adhesion of potentially pathogenic bacteria to
the intestinal epithelia (He et al., 2007). In addition, breastfed infants show greater
diversity in the *Bifidobacteria* populations than that of formula-fed infants, and exhibited
greater microbial diversity increases with weaning than formula-fed infants. In addition,*Bifidobacteria* and *Bacteroides* are thought to have an inverse relationship with one
another (Albenberg and Wu, 2014). Since IBD is associated with decreased biodiversity of the intestinal microbiota and increased amounts of *Bacteroides* (Kostic et al., 2014),
and changes in infant feeding practices may play an important role in altering the gut microbial environment, it follows that IBD risk may be related to breastfeeding practices.

In the United States, these cultural changes to infant feeding practices may be able to at least partially explain the trends in IBD incidence and prevalence rates.

Epidemiological studies suggest that the incidence rates of IBD have been increasing in the United States since the early 1950s (Lakatos, 2006). At about the same time, breastfeeding in the United States began to decline, and cow’s milk and other early foods began to replace breastmilk at a younger age. Although breastfeeding began increasing again in the 1970s, this was also accompanied by an increase in formula fed infants after 4 months of age. By 1980, there was a 30% increase in the number of 6-month-old formula-fed infants, and this percentage continued to increase through the 1990s (Fomon, 2001). Though it is possible that the relationship between these trends are coincidental, a meta-analysis of breastfeeding and the risk of IBD supported the hypothesis that breastfeeding was associated with a reduced risk of both UC and CD (Klement et al., 2004). In addition, a study conducted on over 400 IBD patients and over 900 control individuals from eight countries in Asia and in Australia found a strong protective relationship between breastfeeding and reduced IBD development when infants were
breastfed for 12 months or longer. This was hypothesized to be due to the effects of breastfeeding on the development of the intestinal microbiome (Ng et al., 2015).

Based on the above evidence, it is highly likely that a decrease in breastfeeding is somehow linked to the increase in IBD risk. However, many of the studies that have been conducted on the correlation between breastfeeding and IBD fail to define the duration and exclusivity of breastfeeding practices (Klement et al., 2004). Since studies have suggested that the length of breastfeeding is important to disease prevention (Ng et al., 2015), future research on the link between breastfeeding and IBD should better define both the duration and exclusivity of breastfeeding.

**Appendectomy**

Although it was once considered a vestigial organ, the appendix is now being studied as an organ of evolutionary and medical importance. In IBD, appendectomies have been linked to changes in the risk of disease development. Interestingly, undergoing an appendectomy before 20 years of age leads to an increased risk of CD, but a decrease in the risk of UC (Loftus, 2004). The reason for this difference in risk is not understood (Scaldaferri et al., 2013). Nevertheless, many Asian countries cite increasing incidence rates of appendicitis and appendectomies as a risk factor for IBD (Ng et al., 2015). Unfortunately, cultural analysis of appendicitis and appendectomy rates are sparse, thus the relationship between appendectomy and IBD will be examined here from a mostly biological perspective.

A recent meta-analysis by (Ferris et al., 2017) has shown that although the rates of appendicitis and appendectomies have stabilized or started to decrease in Western
countries, these rates are increasing rapidly in newly industrialized countries. Thus, there seems to be a correlation between industrialization, appendicitis, and IBD. Although untangling the correlative from the causative factors may be difficult, examining the role the appendix plays in intestinal health from an evolutionary perspective may be able to elucidate the effects of industrialization on the appendix and consequent risk of IBD.

It is now thought that the appendix helps to modulate intestinal immune health. In addition, the appendix is thought to play an important role in immune function. Pathogenic (Scaldatá et al., 2013), have been shown to regulate epithelial regeneration and protect against potential pathogens. Known as biofilms, which are periodically shed into the large intestine, these biofilms in healthy individuals, the gut microbiota of the appendix form microbial communities known as biofilms. Gut microbiota and harbor commensal gut microbes (Bollinger et al., 2007).

A molecular-level investigation into this protective role of the gut microbiota has been shown to introduce much (a glycoprotein that protects intestinal surfaces) and IgA due to its association with a large amount of lymphoid tissue. This lymphoid tissue has been shown to regulate intestinal immune health. In addition, the appendix has been shown to be an important component of mucosal membranes. It is hypothesized that this lymphoid tissue helps to modulate intestinal immune health.

In healthy individuals, the gut microbiota of the appendix form microbial communities known as biofilms, which are periodically shed into the large intestine. These biofilms have been shown to regulate epithelial regeneration and protect against potential pathogens. It is now thought that the appendix helps to modulate intestinal immune health. This lymphoid tissue has been shown to introduce much (a glycoprotein that protects intestinal surfaces) and IgA due to its association with a large amount of lymphoid tissue. It is hypothesized that this lymphoid tissue helps to modulate intestinal immune health.

Although the correlation between industrialization, appendicitis, and IBD seems to be a correlation between industrialization, appendicitis, and IBD, newly industrialized countries. Thus, there are countries where rates are increasing rapidly in newly industrialized countries.
There are two hypotheses for why removal of this beneficial organ may result in a protective effect against UC. The first is that appendectomy removes specific intestinal microbial species that cause inflammatory responses in patients with UC (Jackson et al., 2014). The second hypothesis suggests that there might be a distinct microbial composition of the appendix that predisposes individuals to appendicitis but protects against UC. However, the exact bacterial mechanisms behind this remain unknown (Ananthakrishnan, 2015; Jackson et al., 2014). Nevertheless, these hypotheses might also help to explain why risk of CD may increase after an appendectomy. Still, research on the effects of appendectomy on intestinal health are relatively scarce, and there is conflicting evidence pertaining to the benefits of appendectomy for patients with UC (Parian et al., 2017). Future research should be conducted in order to clarify the exact role that the appendix plays in shaping the intestinal microbiome and in modulating intestinal immune health.

**Antibiotics**

The discovery of penicillin in 1928 led to a medical revolution that saved the lives of many from life-threatening infections (Neuman et al., 2018). Nonetheless, childhood antibiotic exposure has been identified as a risk factor for IBD and is associated with dysbiosis of the gastrointestinal microbiome (Francino, 2016; Kaplan, 2015; Lewis et al., 2015). Broad-spectrum antibiotics affect the abundances of 39% of the bacteria in the gut, and antibiotic-induced changes can remain for months to years after initial treatment. Although the microbiome may eventually return to a composition similar to that of the composition before antibiotic treatment, the original composition is never fully recovered.
Antibiotics may even be used to treat IBD (Salaga et al., 2014); thus, it is important to understand how antibiotics affect the gut microbiota.

Antibiotics are the most prescribed medication in neonatal and pediatric populations in the US (Gibson et al., 2015; Neuman et al., 2018). When given before birth, antibiotics have been shown to alter the mother’s microbiome, and can cross the placenta and enter the fetus, which may affect the initial inoculation of the infant. Prenatal maternal antibiotics are prescribed for urinary tract infection, sinus infections, ear infections, and other bacterial infections. In addition, peripartum antibiotics are often given for prolonged rupture of membranes, Group B streptococcus colonization, C-section, or chorioamnionitis, and postpartum antibiotics may be prescribed for endometritis, surgical site infections, and mastitis. Additionally, pre-, peri-, and postnatal antibiotic usage is extensive among breastfeeding mothers (Lemas et al., 2016). Subtherapeutic antibiotic exposure in infancy, such as through breastmilk, may also affect the developing microbiome. Mice exposed to subtherapeutic antibiotics in drinking water had a significant decrease in the ratio of Bacteroides to Firmicutes, but no overall change in the bacterial load (Gibson et al., 2015). Furthermore, human infants whose mothers received antibiotics during labor and delivery to prevent infection had microbiomes that were significantly different than that of infants whose mothers did not receive treatment (Arboleya et al., 2015). Additionally, low birthweight newborns whose mothers had been given antibiotics to prevent Group B streptococcus infection had an increase in *Escherichia coli* (Ledger and Blaser, 2013), and preterm infants treated with antibiotics and infants whose mothers received antibiotics had low abundance of *Bifidobacterium* and low bacterial diversity, which correlated with the onset of
necrotizing enterocolitis (Francino, 2016). Necrotizing enterocolitis is an inflammatory disease that primarily affects the bowels of preterm infants (although similar symptoms can appear in term and late-term infants), and has an estimated rate of death between twenty and thirty percent (Neu and Walker, 2011). Therefore, understanding how antibiotics affect the intestinal microbiome may shed light on how they may lead to the development of inflammatory bowel disorders.

A longitudinal study of 39 children during their first three years of life compared the microbial diversity of antibiotic treated and untreated children. Those children who were treated with antibiotics had decreased microbial diversity and increased short-term composition changes of their gut microbiota. In addition, antibiotic treated children had less stable gut microbiomes than untreated children (Yassour et al., 2016). A study on 142 Finnish children aged two to seven found that antibiotics disrupt microbial composition and metabolism. Compared to untreated children, children who received antibiotics had an increase in members of the Bacteroidetes and Proteobacteria phyla (including Enterobacteriaceae) and a decrease in members of the Actinobacteria phyla, including Bifidobacteria (Korpela et al., 2016).

Antibiotic exposure in childhood may also alter immune response, causing abnormal inflammatory responses that can create dysbiosis of the gut microbiome (Lewis et al., 2015). Antibiotics have been observed to alter the stimulation of NOD1 and Toll-like receptors (molecules that sense microorganisms in the early innate immune response), which can affect lymphoid (immune system) tissue development, T-cell (white blood cell) differentiation, neutrophil (innate immune system white blood cells) priming, production of antibacterial compounds, and cytokine (cell-signaling molecules) release
In mice, early exposure to antibiotics triggered a stress response that increased corticosterone levels and led to an enhanced function of CD4+ T cells, which ultimately caused a rapid onset of IBD (Scheer et al., 2017).

Although antibiotics have saved countless lives, the use of these medications is not without consequences, as they have been found to cause disruption of the microbiota and the immune response. Although the adult microbiome is thought to be able to recover from a single antibiotic exposure within two weeks, multiple treatments can impair recovery. As with any ecosystem, repeated perturbations of the microbiome are especially harmful if it is not given time to recover (Yassour et al., 2016). Therefore, repeated antibiotic exposure in infancy and childhood could cause irreparable damage to a developing gut ecosystem. This, combined with an altered immune response, is thought to increase IBD risk.

Environmental Radiation

Following the atomic bombings of Nagasaki and Hiroshima, there was a significant increase in the number of individuals with digestive diseases (Preston et al., 2012). In areas where nuclear accidents have occurred, such as the Chernobyl Exclusion Zone in Ukraine, animals like bank voles (Myodes glareolus) have been observed to have altered microbiome compositions and functions (Lavrinienko et al., 2018). However, continuous low-dose radiation not resulting from nuclear accidents or events may also impact host-microbial interactions. Low-LET (linear energy transfer) radiation, from X- or γ-irradiation, indirectly affects cells by producing reactive oxygen species (ROS) that can cause DNA and protein damage and can trigger stress responses in microbial and host
cells (Zhang and Steen, 2018). Therefore, radiation exposure may lead to altered immune responses and dysbiosis of the microbiome that could result in IBD.

Radiation enteropathy, which can arise in patients receiving abdominal or pelvic radiotherapy for cancer, includes symptoms such as malabsorption, bloating, diarrhea, dehydration, abdominal pain, anorexia, nausea, and vomiting (Packey and Ciorba, 2010). Many of these symptoms are similar to those observed in IBD patients. Furthermore, in both IBD and radiation enteropathy, the expression of cytokines (cell-signaling molecules) including interleukin 1β (IL-1β), TNFα, and TGFβ is increased, and the microbiome is altered (Ferreira et al., 2014). In mice, localized dysbiosis caused by radiation therapy promotes mucosal IL-1β secretion, which can contribute to radiation-induced tissue damage and inflammation and renders germ-free mice more susceptible to DSS-induced colitis and radiation damage (Gerassy-Vainberg et al., 2018). In addition, patients with IBD are more likely to develop radiation enteropathy, and the microbial profiles of individuals prior to radiation therapy may determine if the patient develops radiation enteropathy (Packey and Ciorba, 2010).

It is unclear as to whether a dysregulated inflammatory response causes gastrointestinal dysbiosis or if dysbiosis initiates an inflammatory response leading to IBD. Research on radiation enteropathy, which has symptoms similar to IBD, has suggested that the dysbiosis precedes the inflammatory response (Gerassy-Vainberg et al., 2018). However, other investigators have suggested that increased TNFα levels resulting from radiation exposure can increase intestinal permeability and apoptosis and make the epithelium more susceptible to pathogenic bacteria (Ferreira et al., 2014). It is
possible that a combination of dysbiosis caused by external factors and an altered immune response are responsible for IBD onset.

Due to the nature of the disease, patients with IBD are exposed to higher amounts of radiation from diagnostic imaging, such as CT scans, than patients with other gastrointestinal disorders (Desmond et al., 2012). Not only does this increase the risk of malignancy in this population (Desmond et al., 2012; Newnham et al., 2007), but given that continuous radiation exposure can lead to disruption of the immune response and microbial ecosystem of the gut (Zhang and Steen, 2018), repeated radiation exposure from diagnostic imaging may worsen symptoms in IBD patients. It is thus important to reduce the amount of radiation exposure from diagnostic imaging in IBD patients.

Treatments for IBD

Although there is no cure for IBD, there are a number of treatments available. Current treatments primarily target abnormal host immune responses (Celiberto et al., 2018). In Western societies, IBD patients are most concerned with the course of the disease, possibility of ostomy surgery, medication side-effects, and disease complications (Levenstein et al., 2001). As IBD becomes a global disease, it will be increasingly important to develop treatments that efficiently combat symptoms with the fewest side-effects.

Current treatments for IBD include corticosteroids, immunosuppressive drugs (such as 5-aminosalicylic acid), immunomodulators (such as azathioprine and methotrexate), and biologics (Celiberto et al., 2018; Mulder et al., 2014; Salaga et al., 2014). Biologics are antibodies that inhibit inflammation through targeting pro-
inflammatory cytokines tumor necrosis factor-α (TNF-α) or interleukin-12 (IL-12)/23p40, or preventing immune cell recruitment in the gut (Celiberto et al., 2018). Biologics are often used when other treatments fail (Wentworth et al., 2018) and have become of great interest to researchers developing IBD treatments (Mulder et al., 2014). However, biologics and steroids can lead to increased risk of infection or cancer (Celiberto et al., 2018). Therefore, there is a need for better treatment options for IBD.

Alterations to the Microbiome (Probiotics and Fecal Microbiota Transplants)

Although the most common treatments for IBD target pathological immune responses, therapies that treat dysbiosis of the gut microbiome have also been considered. These therapies include probiotics and fecal microbiota transplants (FMT). In both probiotic therapy and FMT, live microorganisms are used to improve patient health outcomes through temporary alteration of the gut microbiome (Celiberto et al., 2018; Goyal et al., 2018).

Probiotics have been suggested as a possible therapy for IBD due to their ability to provide host organisms with certain health benefits. The Food and Agriculture Organization/World Health Organization (FAO/WHO) describes probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” (Jensen et al., 2012). *Lactobacillus casei* Shirota was found to restore normal stimulatory capacity of dendritic (antigen-presenting immune) cells in patients with UC by reducing the expression of toll-like receptors (proteins expressed on immune cells that recognize microbial compounds and initiate immune response) TLR2 and TLR4. In mice, a combination of eight different probiotic strains have been shown to reduce disease activity and inflammation with dextral sulphate sodium (DSS) colitis (experimentally-
induced colitis in animal models). Furthermore, *L. plantarum* 299V and *L. plantarum* VSL#3 have been shown to prevent colitis development and improve colitis and disease activity in IL-10-deficient mice (Celiberto et al., 2018). However, in humans, probiotics have no benefit when compared to placebo in inducing remission of active UC, preventing relapse of UC or CD, or preventing clinical or endoscopic relapse of post-operative CD (Derwa et al., 2017). The lack of clinical success may be attributed to an inefficient one-size-fits-all approach, the inability of new organisms to take up a permanent residence in the gut, and an inflamed intestinal environment that is inhospitable for many probiotic organisms (Celiberto et al., 2018).

Fecal microbiota transplants have also been posited as potential therapies for restoring the gastrointestinal microbiome of IBD patients to a healthy state. Fecal microbiota transplants involve the transplant of fecal or stool matter from a healthy donor to a patient’s GI tract to restore healthy conditions, and was labeled by the FDA as an Investigational New Drug for IBD in 2016. Aside from restoring microbial organisms to the gastrointestinal tract, FMT improves immune function by regulating inflammatory markers through the inhibition of T cell, leukocyte adhesion, and the production of inflammatory markers. In addition, FMT helps to reduce permeability of the epithelial barrier by increasing the number short-chain fatty acid producing microorganisms (Sunkara et al., 2018). A study assessing the safety, clinical response, and changes in the gut microbiome to FMT in children with UC, CD, and indeterminate colitis found that 57% of patients demonstrated clinical response at one month, 28% demonstrated clinical response at six months, and two patients with CD were at remission at six months post-transplant. Although patients had an increase in intestinal species diversity at one month,
most of these changes shifted back toward the baseline by six months. Therefore, FMT can create short-term changes in patients with active IBD; however, more research must be conducted to determine if any of these effects can be long-lasting (Goyal et al., 2018).

Complementary and Alternative Medicine

Complementary and alternative medicine (CAM) products include herbal medicine, dietary supplementation, and mind-body medicine, such as acupuncture, moxibustion (a traditional Eastern medicine therapy that involves burning dried moxa, a plant related to mugwort, on or near a person's skin), and hypnotherapy. It is estimated that the prevalence of current and past use of CAM in North America and Europe ranges from 21-60%. Those patients with IBD who are of younger age, female, have achieved a higher education level, and have experienced adverse drug reactions from IBD treatments (such as extra-intestinal manifestations of IBD and psychological stress as the result of their medications and/or prolonged, intense steroid use) are more likely to use CAM. Furthermore, a study in Germany found that 48% of IBD patients believed that a scientific foundation of CAM was important and 65% of IBD patients reported that they would continue to use CAM even if scientific reports showed it to be ineffective (Ng et al., 2013). Given the popularity of CAM, both in Eastern and Western societies, it is important to understand their efficacy in treating IBD.

A number of herbal therapies have been observed to be superior to the placebo in treating IBD symptoms. One of these herbal therapies is Aloe Vera gel, which is believed to have anti-oxidant, anti-inflammatory, anti-ageing, anti-cancer, immune boosting, and other healing properties and has been used by Egyptian, Chinese, Indian, and European
cultures for over 5000 years to treat skin and digestive diseases (Langmead et al., 2004). In addition, treatment with wheatgrass juice (*Triticum aestivum*), which was popularized in the United States by Dr. Ann Wigmore more than 40 years ago as a therapy for chronic inflammatory disorders and other illness, has been shown to reduce disease activity in patients with active UC (Ben-Arye et al., 2002). The traditional Chinese medicines *Andrographis paniculata* extract (HMPL-004) (traditionally used to treat infections), Xilei-san (traditionally used to treat ulcerations of the pharynx, tongue, and mouth), and *Tripterygium wilfordii* (used to treat autoimmune and inflammatory disorders) have also demonstrated therapeutic properties (Ren et al., 2013; Salaga et al., 2014; Zhang et al., 2013). Furthermore, wormwood (*Artemisia absinthium*), a traditional medicine used for centuries in Europe to treat a wide variety of ailments, performs better than placebo in treatment of CD symptoms and has been shown to improve the mood of patients with CD (Krebs et al., 2010) (Table 1).

Some herbal therapies have been shown to be as effective as common allopathic treatments for IBD. In particular, *Boswellia serrata* gum resin and *Plantago ovata* have been observed to be as effective as mesalazine (a common allopathic medicine) in treatment of UC (Ng et al., 2013). The medicinal properties of *Boswellia serrata* resin (commonly known as frankincense) were first described by the Egyptians in the Ebers papyrus around 1500 BCE, and it is now used for a variety of medicinal purposes around the world. In Kenya, *Boswellia serrata* resin is used to treat wounds and prevent blood loss from schistosomiasis infection. It is used in China to treat skin infections and bruises and in Ethiopia as a tranquilizer. In India, *Boswellia resin* is used to treat a number of inflammatory disorders, including Crohn's disease (Moussaieff and Mechoulam, 2009).
Plantago ovata seeds are used in traditional medicine in Asia as a source of fiber to improve intestinal functions (Goncalves and Romano, 2016) (Table 1).

**Table 1: Herbal therapies found to improve IBD symptoms.**

<table>
<thead>
<tr>
<th>Herbal Therapies</th>
<th>Country/Continent Where it is used</th>
<th>Traditional Uses</th>
<th>Performs Better Than</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe Vera Gel</td>
<td>Egypt, China, India, Europe</td>
<td>Anti-oxidant, anti-inflammatory, anti-ageing, anti-cancer, immune boosting</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wheatgrass Juice (Triticum aestivum)</td>
<td>United States</td>
<td>Treatment of chronic inflammatory diseases</td>
<td>Placebo</td>
</tr>
<tr>
<td>Andrographis paniculata extract (HMPL-004)</td>
<td>China</td>
<td>Treatment of infection</td>
<td>Placebo</td>
</tr>
<tr>
<td>Xilei-san</td>
<td>China</td>
<td>Treatment of ulcerations on tongue, mouth, and pharynx</td>
<td>Placebo</td>
</tr>
<tr>
<td>Tripterygium wilfordii</td>
<td>China</td>
<td>Treatment of immune disorders</td>
<td>Placebo</td>
</tr>
<tr>
<td>Wormwood (Artemisia absinthium)</td>
<td>Europe</td>
<td>Treatment of a variety of ailments</td>
<td>Placebo</td>
</tr>
<tr>
<td>Frankincense (Boswellia serrata resin)</td>
<td>Kenya, Ethiopia, China, India</td>
<td>Treatment of wounds, blood loss, skin infections, bruises, and inflammatory disorders. May be used as a tranquilizer (Ethiopia)</td>
<td>Mesalazine</td>
</tr>
<tr>
<td><em>Plantago ovata</em> seeds</td>
<td>Asia</td>
<td>Improve intestinal function</td>
<td>Mesalazine</td>
</tr>
</tbody>
</table>

Dietary supplementation is also common among IBD patients. Dietary supplementation includes probiotics, prebiotics, and fish oil (Ng et al., 2013). Prebiotics
are substances that are selectively used by host microorganisms and confer a health benefit to the host. Prebiotics include inulin-type fructans, galacto-oligosaccharides, lactulose, β-glucans, arabinoolxylan oligosaccharides, xylo-oligosaccharides, soy bean oligosaccharides, isomalto-oligosaccharides, and pectin, most of which are sugars that come from plants. However, prebiotics have not been shown to consistently improve or worsen IBD symptoms (Celiberto et al., 2018). Omega-6 (n-6) and omega-3 (n-3) polyunsaturated fatty acids (PUFA) found in fish oil are thought to mediate immune and inflammatory responses, and increased intake is thought to reduce inflammation and reduce the risk of IBD (Wall et al., 2010).

Discussion

The ability of the gastrointestinal microbiome to undergo rapid changes in response to environmental changes has been hypothesized to help the host meet physiological demands (Amato et al., 2015a). In fact, the composition of the microbiota may be shaped more by the environment than by the host’s genetics. Adult monozygotic twins have microbiomes that are no more similar in composition than adult dizygotic twins. In addition, genetically unrelated cohabitating spouses have microbiomes that are significantly more similar to one another than members of different households (Yatsunenko et al., 2012). Furthermore, dogs (*Canis lupus familiaris*) have microbiomes that are more similar to humans than the microbiomes of pigs or mice, and they exhibit a similar response to dietary changes. The observed similarity between the dog and human microbiomes is most likely due to shared environments and lifestyles (Coelho et al.,
2018). Therefore, as humans alter the visible environment, microbial ecosystems (like those within the gut) are also likely affected.

One result of industrialization is better access to healthcare and improved diagnostic technology. This has been associated with increased incidence and prevalence rates of IBD (Kaplan, 2015). Although this may be associated with an increase in the number of patients diagnosed with IBD, it cannot explain the initial cause of the disease. Since IBD has been linked to a relationship between environmental factors, the intestinal microbiome, and host biology (Kostic et al., 2014; Loftus, 2004), the relationship between these factors should be elucidated.

According to the hygiene hypothesis, industrialization may have led to the loss of key regulatory members, including helminths. Once ubiquitous in human gastrointestinal tracts, these worm-like parasites have evolved mechanisms for down-regulating intestinal immune responses. In the absence of helminths, these immune responses are able to operate at full capacity, ultimately resulting in immune dysfunction. It has been suggested that reintroducing these members or their regulatory molecules to the gastrointestinal tract may help to reduce the risk of developing IBD (Weinstock and Elliott, 2009).

One environmental factor that is often linked to IBD risk is diet. From an evolutionary standpoint, taxonomic shifts in the composition of the microbiome may have improved energy production and fat storage in early humans. However, these changes may have also made humans more susceptible to obesity and metabolic and immune disorders in times when food is abundant (Amato et al., 2015b; Celiberto et al., 2018). Further, diets high in indigestible fiber support the growth of bacteria known to produce short-chain fatty acids, which help protect against intestinal inflammation (De
Filippo et al., 2010). Since urbanization leads to diets high in sugar, animal fats and proteins, and processed foods (Drewnowski and Popkin, 1997), it is likely that dietary shifts are causing changes in the microbiome that increase the risk of obesity, metabolic disorders, and inflammatory diseases.

Breastfeeding has also been associated with IBD risk. However, there have been contradictory results about the relationship between breastfeeding and IBD (Ng et al., 2015). Nevertheless, breastfeeding is thought to protect against IBD by promoting the growth of beneficial bacteria that prevents intestinal inflammation and the adhesion of pathogens to the gut epithelium (Klement et al., 2004). Breastmilk contains human milk oligosaccharides that promote the growth of *Bifidobacteria*, which produce Immunoglobulin A (Albenberg and Wu, 2014), an antibody that helps protect against pathogens (He et al., 2007). Therefore, the usage of formula that does not contain human milk oligosaccharides may affect the growth of *Bifidobacteria* in the gut. This may affect the production of certain immune molecules in the gut, such as Immunoglobulin A, and increase the risk of chronic immune disorders, such as IBD.

Like breastfeeding, there is conflicting evidence for whether or not appendectomy prevents the development of IBD. Although it may protect against UC, it is associated with an increased risk of CD. The reasons for this are not well known (Loftus, 2004), but it may be associated with the evolutionary role of the appendix. Despite once being considered a vestigial organ, the appendix is now thought to have a number of functions, including the production of immunomodulatory molecules and protection of beneficial organisms (Bollinger et al., 2007). Appendectomy may therefore result in changes in both
immune function and the gut microbiome, possibly leading to a chronic inflammatory response.

High antibiotic exposure in childhood has been associated with dysbiosis of the microbiome and increased risk of IBD (Francino, 2016; Kaplan, 2015; Lewis et al., 2015). Antibiotics have also been shown to negatively impact immune function (Scheer et al., 2017). Even if the microbiome is thought to be able to largely recover two weeks after antibiotic exposure (Yassour et al., 2016), some changes may continue to last for years (Francino, 2016). Repeated exposure to antibiotics may prevent full recovery of the gut ecosystem. Dysbiosis combined with an impaired immune response as a result of excessive antibiotic use may increase IBD risk.

Low-dose radiation exposure may also increase risk of IBD or worsen symptoms in patients with IBD. Like antibiotics, radiation exposure can lead to dysbiosis of the gut microbiome (Gerassy-Vainberg et al., 2018). Radiation exposure can lead to genetic and protein damage in host and bacterial cells (Zhang and Steen, 2018) and has been shown to disrupt the immune response (Ferreira et al., 2014). Disruption of both the intestinal ecology and host biology due to radiation exposure may worsen inflammatory responses and lead to chronic illness.

As with any environmental stressor, humans have begun attempting to reduce the negative symptoms that occur with IBD. For the most part, behavioral adaptations in terms of medicinal treatments are used to alleviate IBD symptoms. Many of these treatments affect the composition of the gut microbiome and/or the immune response. Given that a number of environmental factors have been associated with disease
development, it may be helpful to pursue treatment options that reduce the impact of these factors.

Like all organisms, humans adapt and acclimatize to changing environments. It is possible that repeated perturbations to the gastrointestinal ecosystem caused by external factors associated with industrialization may create a change in the environment to which the body must adapt. The chronic inflammatory response observed in IBD is likely induced both by external factors outside of the gut and internal factors within the gut. Inflammation can cause further dysbiosis of the gut microbiome, which can in turn lead to a greater inflammatory response (Celiberto et al., 2018), eventually resulting in chronic inflammation of the gastrointestinal tract. Nevertheless, some of these factors (antibiotics, radiation exposure) have also been shown to impact the immune response. Furthermore, there is a discrepancy as to whether dysbiosis precedes a disrupted immune response or if a disrupted immune response precedes dysbiosis (Gerassy-Vainberg et al., 2018). In this case, it may be helpful to examine IBD through an evolutionary systems theory in which a change in one factor affects all other factors. Future studies should examine the ways in which the environment, intestinal microbiome, and host biology interact.
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