Check for updates

A Review of Inflammatory Bowel Disease: A Model of Microbial, Immune and Neuropsychological Integration

P. Tavakoli[1]*, U. Vollmer-Conna[2], D. Hadzi-Pavlovic[2] and M. C. Grimm[1]

[1]St George and Sutherland Clinical School, Sydney, NSW, Australia, [2]School of Psychiatry, University of New South Wales, Sydney, Australia

Objective: Inflammatory bowel diseases (IBDs) are complex chronic inflammatory disorders of the gastro-intestinal (GI) tract with uncertain etiology. IBDs comprise two idiopathic disorders: Crohn's disease (CD) and ulcerative colitis (UC). The aetiology, severity and progression of such disorders are still poorly understood but thought to be influenced by multiple factors (including genetic, environmental, immunological, physiological, psychological factors and gut microbiome) and their interactions. The overarching aim of this review is to evaluate the extent and nature of the interrelationship between these factors with the disease course. A broader conceptual and longitudinal framework of possible neuro-visceral integration, core microbiome analysis and immune modulation assessment may be useful in accurately documenting and characterizing the nature and temporal continuity of crosstalk between these factors and the role of their interaction (s) in IBD disease activity. Characterization of these interactions holds the promise of identifying novel diagnostic, interventions, and therapeutic strategies.

Material and Methods: A search of published literature was conducted by exploring PubMed, EMBASE, MEDLINE, Medline Plus, CDSR library databases. Following search terms relating to key question were set for the search included: "Inflammatory bowel diseases," "gut microbiota," "psychological distress and IBD," "autonomic reactivity and IBD," "immune modulation," "chronic inflammation," "gut inflammation," "enteric nervous system," "gut nervous system," "Crohn's disease," "Ulcerative colitis", "depression and IBD", "anxiety and IBD", "quality of life in IBD patients," "relapse in IBDs," "remission in IBDs," "IBD disease activity," "brain-gut-axis," "microbial signature in IBD," "validated questionnaires in IBD," "IBD activity indices," "IBD aetiology," "IBDs and stress," "epidemiology of IBDs", "autonomic nervous system and gut inflammation", "IBD and environment," "genetics of IBDs," "pathways of immune response in IBDs," "sleep disturbances in IBD," "hypothalamic-pituitary-adrenal axis (HPA)," "sympatho-adrenal axis," "CNS and its control of gut function" "mucosal immune response," "commensal and pathogenic bacteria in the gut," "innate and adaptive immunity." Studies evaluating any possible associations between gut microbiome, psychological state, immune modulation, and autonomic function with IBDs were identified. Commonly cited

published literatures with high quality research methodology/results and additional articles from bibliographies of recovered papers were examined and included where relevant.

Results: Although there is a substantial literature identifying major contributing factors with IBD, there has been little attempt to integrate some factors over time and assess their interplay and relationship with IBD disease activity. Such contributing factors include genetic and environmental factors, gut microbiota composition and function, physiological factors, psychological state and gut immune response. Interdependences are evident across psychological and biological factors and IBD disease activity. Although from the available evidence, it is implausible that a single explanatory model could elucidate the interplay between such factors and the disease course as well as the sequence of the effect during the pathophysiology of IBD.

Conclusion: Longitudinal monitoring of IBD patients and integrating data related to the contributing/risk factors including psychological state, physiological conditions, inflammatory/immune modulations, and microbiome composition/function, could help to explain how major factors associate and interrelate leading to exacerbation of symptoms and disease activity. Identifying the temporal trajectory of biological and psychosocial disturbances may also help to assess their effects and interdependence on individuals' disease status. Moreover, this allows greater insight into understanding the temporal progressions of subclinical events as potential ground for disease severity in IBD. Furthermore, understanding the interaction between these risk factors may help better interventions in controlling the disease, reducing the costs related to disease management, further implications for clinical practice and research approaches in addition to improving patients' mental health and quality of life.

Keywords: IBD, neuropsychology, immunology, microbiome, physiology, autonomic nervous system, IBD therapeutic

INFLAMMATORY BOWEL DISEASES

Introduction

Inflammatory Bowel Diseases (IBDs) are debilitating chronic inflammatory disorders of the gastrointestinal tract with the peak age of onset in adolescence and young adulthood [1]. IBDs are complex chronic inflammatory disorders with multiple factors such as psychological distress, autonomic dysfunction, gut microbiome dysbiosis and immune modulations associated with disease activity. The incidence of IBDs has shown an increasing trend over the last few decades. This was initially noted in Western countries and is now being increasingly observed in countries such as Japan, China and India [2]. IBDs are recognized as a serious, worldwide public health issue with an increasing economic and financial burden. This review has several key aims including 1) to present an overview on IBDs, the disease course and immune modulations in IBD, 2) to outline the importance of the autonomic nervous system and its possible association with chronic inflammatory conditions such as IBDs and their symptomatology, 3) to examine the impact of psychological factors and IBD, and 4) to address the role of gut microbiota and its interplay with disease activity.

Inflammatory bowel diseases: IBDs are characterised by chronic inflammation of the GI tract and comprise two idiopathic gastrointestinal disorders known as ulcerative colitis (UC) and Crohn's disease (CD). Despite intense research efforts, the disease aetiology (ies) is (are) not fully understood. However, it appears that both genetic and environmental factors are involved in IBD causation, affecting the interaction between the intestinal mucosa and luminal bacteria, with a breakdown in the regulatory constraints of mucosal immune responses to enteric bacteria. In other words, an immune (inflammatory) response that is too easily triggered and/or needlessly prolonged. Both UC and CD are chronic disorders of a remitting and relapsing kind. Just as the cause of the initial onset of IBD is unknown, what leads to remission and relapse is also uncertain [3].

The incidence of inflammatory bowel diseases is increasing globally and in 2012, the highest reported prevalence values for IBD were in Europe (UC, 505 per 100,000 persons; CD, 322 per 100,000 persons) and North America (UC, 249 per 100,000 persons; CD, 319 per 100,000 persons) [4]. It has been estimated that in developed countries up to 360 in every 100,000 individuals have IBD [5]. The incidence of CD has increased by 70% and incidence of UC has increased by 60% [4] with an increasing trend in Asia since 1988 [6]. There is a high incidence of inflammatory bowel diseases in Australia [7–10]. According to an estimate by Gastroenterological Society of

Australia in 2018, Australia has one of the highest prevalence rates of IBD worldwide with approximately 75,000 Australians diagnosed with IBD and over 1,622 new cases diagnosed every year, 776 with CD and 846 with UC (https://www.gesa.org.au/public/13/files/Clinical%20Updates%20and%20Guidelines/2018_IBD_Clinical_Update_May_update.pdf).

UC is characterised by chronic inflammation of the large intestine with abnormal activation of the immune system. It affects the inner-most layer of the colon and rectum [11]. CD can affect any level of the intestinal tract from the mouth to the anus and across all layers of the bowel wall, but mostly affects lower small intestine (ileum) and colon. The most common symptoms of IBD include diarrhea, rectal bleeding, intermittent nausea and vomiting, and abdominal pain or tenderness [12–14]. The symptoms are due to intestinal damage resulting from the exaggerated inflammatory response. Complications from these immune-mediated diseases include anemia, malnutrition, bowel obstruction, fistula, infection, and an increased risk of colon cancer. Extra-intestinal manifestations may also develop, such as joint problems (arthralgia, arthritis, and ankylosing spondylitis), rashes and skin conditions (erythema nodosum, psoriasis), chronic liver disease (primary sclerosing cholangitis) and eye conditions (such as uveitis). There is no cure for IBD. Clinical management focusses on keeping patients in remission and asymptomatic with a primary aim of reducing inflammation during relapse and secondary aims of prolonging the time spent in remission and mucosal healing.

Contributing Factors in IBDs

IBDs are complex diseases with multiple factors likely to contribute to the aetiology and pathogenesis of the diseases. There is an accumulating body of research exploring potential factors thought to contribute to the etiology of IBDs. Over the last 50 years, but mainly in the last two decades, various advances have brought attention to the mechanisms, and interplay of the underlying factors in IBD disease activities and its progression. Included in these are increased knowledge of cell and molecular biology, deeper insight into the immune response and potential immune cascades in chronic inflammatory disorders as well as breakthrough technologies in genetic analysis of diseases. It is worth highlighting the innovation of genome wide association studies and subsequent omics analyses, together with understanding of the function of gut microbiota in health and disease, as significant advances improving our understanding of disease development. It seems that there is a need to apply a combined approach in studying IBDs to have better understanding of the whole orchestra of complex contributors to the disease, including genetics, as well as microbiome-related, dietary-related, autonomic function, environmental and psychosocial factors, and their longitudinal interplay.

The Role of Genetics in IBDs

What we know about genetic predisposition in IBDs is largely based upon comparative studies that investigated the prevalence of such diseases in first degree family members, relatives of the sufferers as well as on twin studies. These genetic studies have greatly increased our understanding of the pathogenesis of IBDs.

The prevalence of IBDs is higher in the relatives of IBD patients [15]. In 1980, Mayberry looked in to the prevalence of Crohn's disease in families of IBD patients and estimated a 30 fold higher risk of developing IBD in a sibling compared with the normal population risk [16]. Monsen also identified a higher prevalence of UC in first degree family members compared to the general population [17]. Similarly, in twin studies of CD and UC, a strong familial aggregation has been observed in monozygotic twins [15, 18]. Genome-wide association studies (GWAS) have been helpful in identifying hundreds of genetic variants in Crohn's disease and ulcerative colitis [19, 20].

Genotyping studies of IBDs highlighted considerable heterogeneity between, and within, UC and CD, with some genes common to both and some separate. So far more than 200 gene polymorphisms and genetic variants have been identified that are associated with IBDs [21, 22]; many of these genes increase the risk of the development of disease by only a very small amount. Furthermore, approximately 70% of IBD risk loci are shared with other immune-mediated disorders including type 1 diabetes mellitus, celiac disease, rheumatoid arthritis, ankylosing spondylitis, and psoriasis [23]. One-third of loci described confer susceptibility to both CD and UC [24].

The first gene identified to be associated with Crohn's disease was Nucleotide-binding oligomerization domain-containing protein 2 (NOD2). This gene is important in immune stimulation against bacterial invasion [25]. Many other IBD risk alleles are associated with either host response to bacterial invasion, development of adaptive or innate immunity, autophagy pathways, phagocytosis, or mucosal barrier function [3]. Disruption in the function of many of these genes increases the risk of development of inflammatory disorders in addition to IBD. Despite the importance of genetic predisposition, there is no single genetic variant that can explain the fast trend development of IBDs. It is also not clear why most individuals, who carry IBD-associated risk variants, remain healthy while others develop IBD or even develop more than one immune-mediated disease. Clearly, genetics alone cannot explain the susceptibility and progression of IBDs. Therefore, the study of the characteristics and roles of other factors that may interact with genetic vulnerabilities in patients with IBDs is critical.

IBDs and Environmental Factors

There is a wide spectrum of different environmental factors proposed to influence the etiology and disease activities of chronic inflammatory disorders such as IBDs. Population based studies have proposed higher incident of IBDs in urban than in rural populations [26, 27]. Evidence supports the inverse association between risk of IBDs with early life exposure to farm animals, pets, larger family size, greater number of siblings [28, 29], mode of childbirth [30] and breast feeding [31]. All such early exposures are known as important determinants for more diverse gut microbiome in early life as an internal environmental factor [29, 32, 33]. The beneficial interaction between gut microbiome with host genetics and immune system is an important internal environmental factor in disease pathogenesis although, external environmental factors are also strong determinants of health and disease. Diet is a major contributor and has both short-term and

long-term influence on intestinal microbiome which can have influence on risk of incidence of the diseases [34, 35]. Many studies that examined the influence of diet on the course of the disease suggested the strong association between the two [36–39].

While studies have shown the increase in risk associated with smoking in CD [40], current smokers have shown strong inverse risk association between smoking and UC [41–43]. Smoking is associated with more severe disease course, greater risk of immunosuppression use or surgery and more risk of recurrence after surgery in CD patients whereas in UC, smoking cessation is commonly a precipitant for relapse within a year of cessation, current smokers have fewer surgeries, milder disease course and less need for immunosuppressive drugs [44–46]. Studies proposed the divergent effect by appendicectomy on UC suggesting inflammation of appendix might have protective interplay with the disease [47, 48]. Early childhood perturbation of gut microbiota through antibiotic therapy has been proposed to alter the gut immune response and influence the susceptibility to IBDs [49, 50].

One of the most significant current discussions in studying complex diseases is the concept of modernised or westernised lifestyle which associates chronic and complex disorders such as IBDs with rapid industrial changes and their effect on the environment and social behaviour [51]. Decline in the incidence of infectious diseases in developed countries due to improved hygiene standards and infection prevention methods (hygiene hypothesis) [52, 53], has resulted in loss of initial symbiotic relationship between the human host and microorganisms [54]; that mutualism is considered essential in development of human immune responses. High levels of stress as a common constituent of industrialisation and its effect on the immune response, neuroendocrine disturbances and psychological adaptation are of major concern in pathophysiology of chronic and complex inflammatory disorders.

Why Consideration of Psychological Variables in IBD is Important

It is well documented that any chronic disease is associated with a greater burden of psychological stress, depression, anxiety and altered quality of life [5, 55–59]. IBD follows the same model of neuropsychiatric co-morbidities, which are more prevalent during an active disease when the disease is difficult to control [60]. Although it could be projected that illness leads to psychological problems through a uni-directional effect on patients' wellbeing and quality of life, bidirectional interplay between disease factors including systemic and local inflammatory activities and the brain is now a generally accepted hypothesis. The study published in 2018 similarly supported this idea when they observed high anxiety scores in patients with clinically active IBD compared to the time these patients were in clinical remission. Same study suggested patients with quiescent disease activity at baseline but abnormal anxiety score had higher rate of relapse when followed up or needed escalation of their therapy [61]. Psychological states can influence patients' behaviour and their perception of the disease through different neuro-endocrine pathways [62, 63]. The role of stress - conceptualised both as an environmental/psychosocial challenge, as well as an internal stressor such as an evolving illness—has

been investigated in the course of IBD, and it has been shown that stress can aggravate physiological, psychological and environmental vulnerabilities leading to emotional distress and potentially onset of mental and physical disorders [5]. It has been proposed that depression and anxiety are more prevalent in IBD patients with greater associations with IBD disease activity [64, 65]. Depression as a neurobehavioral factor can influence the risk of IBD as a pre-existing contributor, it also can be simply a product of the IBD as debilitating disease [66]. Depression can potentially influence the course of the disease by mediating through autonomic nervous system, predominantly through sympathetic nervous system [67, 68].

Nevertheless, studies on causality of psychological states and IBD symptoms have led to contradictory conclusions [64, 69]. Research has identified some aspects of psychological distress commonly manifested in IBD patients including depression and anxiety [70–73] other investigators did not find any evidence of association between psychiatric disorders and UC/CD disease activity [74, 75]. Some data suggested that both depression and anxiety preceded UC (and not CD) [76], while other literature indicated IBD was not a product of psychological distress [77, 78].

Physiological Factors and Their Role in IBDs

Digestive system functions and homeostasis are modulated through both central (CNS) and enteric nervous system (ENS) influences. Bayliss in 1899 proposed innervations in small intestine and their ability to generate downward movements including swaying motion (known as pendulum movement) accompanied by waves of longitudinal constriction, [79]; the exploration of the remarkable functions of an ENS developed further through the mid-20th century [80], described how new technologies and their applications facilitated our understanding of ENS's complexity and neural connectivity in gut [80]. The bidirectional communication of brain and gut is facilitated by means of various pathways. Brain to gut signaling is through hypothalamic-pituitary-adrenal axis (HPA), and two branches of autonomic nervous system (ANS), sympatho-adrenal axis and descending monoaminergic pathways (spinal reflexes) [81]. Gut to brain signaling (bottom-up signalling) is via primary visceral afferent neurons (extrinsic including vagal and spinal afferent as well as intrinsic afferent neurons), enteroendocrine signaling and immune related signaling to brain [81].

The sympathetic nervous system (SNS) modulates GI function and immune regulation by the close proximity of nerve endings to immune cells such as dendritic cells, B lymphocytes and mast cells [82]. The parasympathetic innervations of GI tract (vagal and sacral parasympathetic divisions) are thought to have an anti-inflammatory, immune modulatory role. An example of such activities is the modulation of macrophage activation through nicotinic acetylcholine receptors [83]. Alterations or dysfunction in the activities of the autonomic nervous system (perhaps related to stress, anxiety and depression) alters autonomic output to the gut and is likely to affect brain-gut signaling, gut function and its immune regulation [5].

Gut Microbiota and IBDs

Study of the gut microbiota composition and its function has become a major area of interest within the field of gastrointestinal

disorders including inflammatory bowel diseases [84–86]. Many studies have addressed the possible link between gut microbiota and a maladaptive immune response in genetically susceptible and environmentally at-risk individuals [87–89]. The inappropriate immune response could be either translated to failure in tolerating the commensal bacteria or immune activation toward altered microbial populations (so-called dysbiosis) or function. Although a considerable literature has grown up around the theme of microbiota and inflammatory bowel diseases, there is inadequate knowledge about whether alterations in gut microbiota play a primary role in development of IBDs or are simply a consequence of chronic inflammation [85, 90–92].

Immune Modulation and Inflammatory Bowel Disease

Introduction

The human immune system plays a critical role in recognition, response and adaptation to countless self and foreign molecules, so its integrity is very important in maintaining and recovering health. There are complex innate and adaptive mucosal immune mechanisms in the gastrointestinal tract that regularly examine the luminal contents and can detect microbial or food antigens and can activate immune pathways. Both innate and adaptive immune mechanisms are integrated with different mediators and immune cells to maintain tolerance, manage low grade inflammation and upregulate during the active phase of gut pathologies, including IBDs [93].

Cells of the immune system including dendritic cells, B cells and macrophages are considered as antigen presenting cells (APCs), which are important in both innate and adaptive immunity and immune homeostasis and are able to secret cytokines and activate innate immunity as well as presenting antigens to cells of the adaptive immune system, therefore relating adaptive and innate immunity pathways [94, 95].

Innate immunity comprises programmed and automatic defence-related elements such as the mucosal barrier, tight junctions of the epithelial cells and control of gut permeability, and secretion of antimicrobial enzymes such as defensins and lysozyme to protect the lamina propria from microbial raids [96]. Cells of the innate immune system form one of the nonspecific defense mechanisms against any invasions and include: macrophages, monocytes, neutrophils and other granulocytes, natural killers (NKs), dendritic cells, mast cells, and innate lymphoid cells (ILCs). Non-immune cells also play important roles: intestinal epithelial cells (IECs), endothelial cells, transforming growth factor-β (TGF-β) releasing stromal cells and mesenchymal cells. Epithelial cells contain and are coated with pattern recognition receptors (PRRs: Toll like receptors–TLRs–and Nucleotide-binding Oligomerization Domain-like receptors–NOD like receptors), which are a key component of the innate immune system and can recognise common repetitive patterns present on Gram-positive and Gram-negative bacteria, viruses, parasites, and fungi [97].

These receptors are sensitive to pathogen associated-molecular patterns (PAMPs) such as bacterial

lipopolysaccharides (LPS) [98], Gram-positive and mycobacterial lipopeptide [99], lipoteichoic acid (LTA) and peptidoglycan (PGN) [100], double stranded viral RNA and bacterial DNA [101], and reactive oxygen species (ROS) induced by commensals [102]. Toll like receptors (TLR) are expressed by IECs in small intestine and colon [103, 104]. Signalling from TLRs leads to epithelial cell proliferation, safeguarding of IEC tight junctions, release of IgA and expression of antimicrobial peptides, regulation of proinflammatory cascades through signaling lamina propria immune cells [105, 106], and production of inflammatory cytokines, in case any products of the bacteria permeate the epithelial layer and are sensed by these receptors [107]. Nucleotide oligomerization domain (NOD1 and NOD2) are additional pattern recognition receptors that are intracellular and are required for defence against invasive enteric pathogens [108]. NOD2 is a primary receptor for muramyl dipeptide (MDP)-an immunoreactive peptide constituent of the cell wall of all gram positive and gram-negative bacteria. This peptide plays an important role in bacterial cell integrity and delineate the bacterial cell shape. Sensing of this peptide by the NOD2 receptor results in secretion of antibacterial peptides like α-defensins from the epithelial cell layer [109].

Activation of PRRs in columnar epithelial cells commonly leads to stimulation of transcription factor NFkB, a protein in cytoplasm of epithelial cells and nearly all cell types [110] that controls transcription of DNA in the nucleus of the cells, and cytokine production as part of its role in innate immunity as well as many other conserved cellular functions related to cell survival, cell growth and development, and apoptosis. Activation of NFkB may occur through various activation mechanisms [111] and eventually initiates a prototypical proinflammatory signaling in intestinal inflammation [112]. Activation of NFkB results in upregulation of proinflammatory factors including adhesion molecules, TNF-α, IL-1, IL-6 and IL-8. These molecules control and regulate immune responses and are important in recruiting leukocytes to the inflamed area [111].

Adaptive immunity presents specific immune responses either through B cell or T cell antigen-specific activation. This immune system covers antibody-mediated immune response (adaptive humoral immunity) and adaptive cell mediated immunity; critical contributors include cytotoxic T cells, effector T cells, regulatory T cells (Tregs), T helper lymphocytes and antibody-secreting B cells. Immune cells of the adaptive immune system are differentiated in Peyers' patches of the small intestine, lymphoid follicles of the colon, or mesenteric lymph nodes [113].

The basic development of the function of the human immune system depends on its interaction with the human microbiome [114]. In all mammals the intestinal lumen is colonised by communities of bacteria that result in biofilm production-the proteolytic cleavage of the outer coating of mucus, which creates a barrier to infection. Any challenge that alters the microbiota composition and suppresses their regrowth can disturb the barrier to allow infection and disease [115]. The thickness of this mucus layer of the epithelium is correlated to bacterial content of the intestine; it is thinner in the proximal small intestine (containing 10^3–10^5 organisms per gram) and is

thicker in the distal small and large intestine (containing 10^{10}–10^{12} organisms per gram). Beneath and between the IECs, the lamina propria is the home of stromal cells, T cells, dendritic cells, macrophages, B cells (IgA producing plasma cells), and intraepithelial lymphocytes. Dendritic cells of lamina propria establish tight junction like structures with epithelial cells to have direct bacterial uptake from the intestinal lumen [116]. They are positioned to reach into the lumen and sample the luminal contents as an important surveillance strategy [117]. Activated dendritic cells then migrate to lymph nodes where they can activate T cells.

Immune Modulation and IBDs

Studies on inflammatory bowel diseases have revealed evidence of breakdown in immune regulatory constraint [116] and immune modulation in active phases of the diseases [118, 119]. IBD is generally believed to be driven by an increased population of effector T cells and increased production of proinflammatory cytokines (such as TNF-α, IL-6, IFN γ). The balance between proinflammatory and immunosuppressive forces can determine the progression of inflammation [120, 121]. It has been suggested that epithelial barrier damage could lead to increased intestinal permeability and the influx of intestinal lumen microbes and antigens into the underlying layer including lamina propria, which is the home for immune cells and mediators [96]. Hence, it seems that immune upregulation in IBDs is an outcome of barrier damage and dysregulated cellular responses, with consequent instigation and progression of inflammation in the lamina propria.

The complex orchestrated cross talk between the immune activation and cytokine secretion, stimulates naïve T cells (homing in peripheral lymphoid tissues and lymph nodes) leading to proliferation and activation of effector T cells and memory T cells. Stimulated effector T cells migrate to intestinal lamina propria and nearby blood and lymphatic vessels. Here, lymphocyte cell adhesion molecules (selectins and integrins), and their ligands located on endothelial cells, mediate homing of effector cells. Activated macrophages stimulate adaptive immunity locally and activated dendritic cells migrate to nearby lymphoid tissue where they arouse a range of T helper cells (CD4+) and cytotoxic T cells (CD8+) as well as assisting the maturation of regulatory T cells. Th17 cells are important in defense against mucosal microbial and fungal infections. The key inducing cytokines for activation of Th17 pathways are IL-1, IL-6, IL-23 and transforming growth factor β (TGF-β). Activated Th17 cells release the proinflammatory IL-17 family of cytokines, which are important in the pathogenesis of human colitis [122, 123]. IL-17 is an important cytokine for recruitment of Treg cells and neutrophils [124]. IL-23 is the principal cytokine that regulates the maintenance and function of Th17 cells. In murine studies, it has been shown that IL-6, TGF-β, IL-1β, IL-23 and the ATP that derives from commensal bacteria (such as segmented filamentous bacteria) are required for Th17 cell differentiation. Recent studies have implicated immune modulation by the microbiota as it has been shown that germ free animals have impairment of Th17 cell development and reduced levels of IL-17 production in the colon [125]. Also, Treg

cells in these animals are not as effective as in conventionally colonised animals [126]. An interesting and repeated finding is that in spite of high concentration of anti-inflammatory cytokines such as TGF-β and IL-10 during the active phase of IBDs, mucosal inflammation persists, which underlines deficient immune regulation and complexity of the immune pathways involved in IBDs [127, 128]. Treg cells regulate the level and function of the proinflammatory cytokines derived from effector T cells, and can direct immune responses [129]. Treg cells widely proliferate in an antigen-specific manner and can respond to both self and foreign peptides. Cytokines released by Treg cells are very important to limit uncontrolled immune responses at environmentally exposed surfaces such as gut. These special T cells play a key role in the maintenance of self-tolerance, therefore preventing autoimmune and inflammatory diseases [129]. Treg cell deficiency results in an effector T-cell response and IBD. This response is driven by reactivity against microbial antigens. Treg cells suppress inflammation through diverse mechanisms including release of inhibitory cytokines such as IL-10, transforming growth factor β (TGF-β), and IL-35 [130]. IL-10 deficient mice maintained in conventional conditions, develop enterocolitis through IL-23 and the Th17 pathway [131, 132].

Much of the current literature on animal models of IBDs pays particular attention to possible links between gut microbiota and mucosal immune responses. Such studies have shown that germ-free mice have an attenuated mucus layer indicating that intestinal microbiota are important in the intensity and function of the mucosal layer [133]. Previous studies have shown that both humans and mice normally tolerate autologous microbiota and the breakdown of this tolerance is associated with chronic intestinal inflammation [134]. It is likely that potential pathological responses to the component of intestinal microbiome, which are restrained by immunoregulatory controls, do occur and when this immune constraint is breached, it modulates the inflammatory response [135]. Also, it is possible that alteration in the composition of gut microbiome toward mainly microbial imbalance and maladaptation of gut microbiota (dysbiosis) disturbs the interaction between the immune system and microbiome and ultimately leads to overemphatic immune responses. These may motivate inflammatory disorders both in and beyond the intestine [136]. Additional observations that suggest possible links between intestinal microbiome and immune response modulation in IBD patients are based on clinical evidence in management of IBD such as patient responses to antibiotic therapy [137–139] and faecal diversion [140–142]. Other investigations identified that IBD patients have higher titres of antibodies against commensal bacteria compared to healthy individuals [143]. Clinically and endoscopically, the distribution of the inflammatory lesions of IBD is more pronounced in the areas of the gut with higher concentrations of bacteria.

Intestinal Microbiome
Introduction

Immediately after birth, environmentally exposed surfaces such as skin, respiratory tract, mouth, vagina and gut are introduced to

and colonised by foreign microorganisms [144]. A large and dynamic community of different bacteria is considered a natural inhabitant of the human gut with well-documented effects on human physiology and pathology arising from the interaction between resident bacteria and the mucosal immune system, though the nature of this symbiosis is not very well understood. It has been suggested that the products of gut microbiome play a big role in intestinal health and homeostasis [145]. Impaired gut microbiota function or composition (dysbiosis) can compromise intestinal function and contribute to intestinal pathology. Gut microbiome is a complex and rich ecosystem that supplies multiple levels of intercellular signaling among host and diverse consortia of bacteria, archaea, fungi, protozoa and viruses. It has been estimated that the human gut microbial cells collectively make up to 10 fold of human cells (almost 10^{14} bacteria/g feces or 100 trillion microbial cells in the human gut) [146–148] and across more than 1,200 distinct microorganisms with more than 7,000 strains [147, 149] (mostly in the large intestine). This community of microbes encoded 100-fold more genes than human genome [144, 150, 151]. The bacterial load is the lowest in upper GI tracts (stomach $0–10^2$, duodenum 10^2, proximal ileum 10^3) and gradually increases by $10^7–10^8$ in distal lumen (terminal ileum) [152–154]. This microbial portfolio can be affected by factors such as genetics, birth route, diet, hygiene, psychological distress, environment and lifestyle, infection and medications especially antibiotics. There are several factors that control the prevalence of bacteria in different parts of the GI tract, such as pH, peristalsis, redox potential, bacterial adhesion, bacterial cooperation, mucin secretion, nutrient availability, diet, and bacterial antagonism [155]. It appears that the cross talk between gut microbiota (composition and their products) and cells of the innate immune system in the gut has led to beneficial cooperation, which has established tolerance toward the commensal microbial community in the gut and is thought to out-compete pathogens. The gene products and metabolic output of the gut microbiota play a big role in dynamics and favourable relationship and beneficial interaction within gut microorganisms themselves and with the host. This relationship is important in sustaining the survival of gut microorganisms in their competitive battle with each other which may have adverse effects on human health [156].

Important roles of intestinal microorganisms in the colonic physiology include their influence on epithelial cell growth and differentiation, absorption (mainly calcium, magnesium and iron) [157] and their metabolites which can be used by the host. Gut-bacteria metabolism accounts for the conversion of many substances into metabolites that can be absorbed and used by the host, including energy and vitamin synthesis [133]. One critical class of metabolites are the short-chain fatty acids (SCFA): propionate, butyrate, and acetates. SCFA are produced through fermentation of undigested carbohydrates by commensal bacteria under the anaerobic condition in the large intestine and through binding to G-protein coupled receptor 43 (GPR43) can be used in selected organs including intestine, adipose tissue and immune cells [158]. SCFA are negatively charged radicals (anions) in the colon and are important as energy sources for proliferation,

growth and differentiation of colonocytes as well as crypt cell differentiation into three lineage (enterocytes, enteroendocrine cells and goblet cells) that migrate to adjoining villi [133, 159, 160]. Butyrate is mainly consumed by colonic epithelial cells and acetate presented systemically [159, 161]. The role of these SCFAs, their signal to gut receptors (Free fatty acid receptor 2–FFAR2, and receptor 3 expressed by enterocytes, enteroendocrine cells and mast cells) [158, 162] and their influence on appetite control and food intake [163] as well as their anti-cancer (especially for butyrate)/anti-inflammatory properties [164] have been rapidly growing areas of research. The increasing promotion of probiotics and prebiotics to assist human health shows recognition of a potential role for beneficial and harmful microbial populations in the aetiology, prevention and control of disease processes [165–168], although data supporting their role in health remain scant.

Most of the initial studies on human gut microbiota were based on standard culture techniques [169] and molecular analysis [170, 171], but more than 90% of the environmental microbes cannot be easily cultured [172], so microbial ecologists developed other culture independent approaches to study microorganisms including using the 16S ribosomal RNA gene (16SrRNA) as a phylogenetic and taxonomic indicator for members of microbial communities [173–175], with further development of novel gene sequencing technologies and availability of powerful bioinformatics analysis. 16SrRNA was the first revolution in culture independent approach in the late 1970s and as a phylogenetic marker to explain microbial structure and diversity [176]. Later metagenomic investigations revealed that the variability of abundance of microbial species in individuals can greatly affect identification of the possible common microbial signature such as prominent clusters comprise some of the most abundant gut species. Such gut species include members of the Firmicutes (~64%) the Bacteroidetes (~23%), the Proteobaceria and the Actinobaceria [149, 154, 177, 178].

The composition of the gut microbiota is shaped by the influence of individual genetics [179], as do other intrinsic and extrinsic host factors, such as diet, drugs, xenobiotics and diseases [180]. The interactions between gut microbiome and host are mutual among individuals but surely not identical. This discrete microbial-host interaction resulted to distinct microbial profile that differentiates one individual from all others [181]. Therefore, in spite of the phylogenetic diversity only a subset of identifiable microbial niches with overlapping functional properties and products but not microbial species, were shared between all individuals which refutes the existence of a "core" microbiome [154, 165, 182, 183].

Although there is evidence showing extensive α and β diversities of human associated microbes [184] and substantial diversity within healthy individuals (mainly among infants) [144, 182, 185, 186], sequence based methods (including 16SrRNA) have confirmed that at phyla level, human gut microbiome is less diverse comparing to other ecosystems (such as soil, ocean water); only limited numbers of bacterial domains are detected in human stool or gut mucosal samples dominated by two bacterial phyla: "Firmicutes" and "Bacteroidetes" (more than 90%) [187, 188].

Such analysis also highlighted other bacterial divisions identified in distal gut as Proteobacteria, Actinobacteria, Fusobacteria and Verrucomicroba [187]. Nonetheless in the lower taxonomic levels (species) there are considerable variations in human gut microbial composition [187, 188].

Gut Microbiome and IBDs

It has long been proposed that gut bacteria play an important role in the pathogenesis of IBD through their direct interaction with the intestinal mucosa. As already mentioned, IBDs are characterised by inappropriate immune upregulation in genetically susceptible patients and it seems that gut microbiota are the target of this inapt immune response either due to loss of tolerance toward commensal bacteria or secondary to an altered microbial diversity and/or function [189]. Animal studies have emerged as powerful platforms for studying the role of gut microbiota in the development of the immune system and immune response. Mombaerts and colleagues showed that transgenic mice expressing aberrant T cell receptors spontaneously develop colitis in response to normal intestinal microbiota [190]. Many subsequent studies present convincing evidence confirming the involvement of the enteric bacteria in pathogenesis of IBD. A range of bacteria are stated to have aggressive or protective functions in intestinal inflammatory disorders such as Crohn's disease; for example phlogistic effects of adherent-invasive *Escherichia coli* [191] and protective effects of Faecalibacterium prausnitzii [192]. In both clinical and experimental cases of IBDs, the abundance of Enterobacteriaceae [193], and Fusobacteria [194] are increased. Other studies have convincingly shown that diversion of the fecal stream induces clinical remission and can prevent recurrence of CD, while infusion of intestinal contents to excluded ileal segments reactivates mucosal lesions [195, 196]. Organ culture of inflamed mucosal samples from patients with active IBD (CD and UC), have confirmed that co-culture with non-pathogenic *Escherichia coli* strains strongly stimulates release of proinflammatory cytokines (IL-6, IL-23p19, IL-12p35, IL-17F, IFN-γ, TNF-α), proinflammatory chemokines (IL-8, CXCL-1 and CXCL-2), which activates the inflammatory cascade, whereas the level of TNF-α and IL-6 was significantly lower in healthy controls or when non-pathogenic *E coli* strains were co-cultured with *Lactobacillus* casei [197, 198]. Studies on mice, rats and guinea pigs have shown increasing evidence that antigens derived from communal bacteria, regulate the immune response as the absence of the healthy community of bacteria in these studies is correlated with non-appearance of intestinal inflammation [199]. To examine the integrated impact of gut microbiota in the pathogenesis of IBDs, it is important to incorporate microbiome data with other data related to immune modulation, genetics, psychological and physiological risk factors.

The Autonomic Nervous System–Connecting the Brain and Body
Introduction

The autonomic nervous system (ANS) is a complex regulatory and signaling system connecting the brain and body. Its function is to maintain homeostasis and facilitate self-regulation and adaptation [200]. The ANS consists of a parasympathetic and a sympathetic division. The parasympathetic nerves subserve vegetative and restorative functions and rest-and-digest activities. The sympathetic system enables energy consuming processes during activity or stress known as the "fight or flight" response to increase endurance and ensure survival. There is a growing body of literature that recognises the role of ANS in chronic disorders as disparate as chronic fatigue syndrome, post-infective fatigue syndrome [201, 202], ischaemic heart disease [203], and chronic depression [204]. In the study of IBDs, a much debated question is whether any disturbance in autonomic function and in bidirectional communications between CNS and gut could establish vulnerability toward persistent functional syndromes and/or chronic gut inflammation [205, 206].

ANS, the Key Body-Brain Connection

The human brain constantly receives signals from the outside environment through different sensory mechanisms [205, 207]. In addition, internal sensory systems collect vital information about the physiological state of multiple physiological microenvironments including any disturbances in gut homeostasis, inflammation, and tissue damage [208–210]. This information is relayed by several afferent neural and endocrine pathways to both autonomic/homeostatic brain centres and to higher limbic and cortical regions. This dynamic processing of information and consecutive cortical integration provides the brain with "conscious awareness" of the internal physiological state-a process known as interoception [208]. The primary interoceptive representation is located in the right anterior insula [211]. The brain's reaction to such information is to adjust descending autonomic regulation, and to alter emotions and motivated behaviour to ensure adaptive survival [208]. The development of human autonomic response pathways throughout evolution has favored sympathetic dominance to increase the chance of survival and adaptive response [212, 213]. Active inhibition executed by prefrontal cortical circuits restrains sympathetic signaling during rest and recovery [214], and through this top-down modulation, it facilitates parasympathetic (vagal) activity. Stressful conditions such as perceived and prolonged psychosocial challenges and adversities, or physiological stressors, such as sickness or inflammation, reduce the prefrontal inhibitory control over sympatho-excitatory circuits, leading to sympathetic dominance and loss of vagal tone [215]. The aim behind this autonomic shift is to enable endurance under challenging conditions. However, prolonged sympthetic hyperactivity engenders a defensive physiological state that lacks dynamic flexibility and this has been associated with poor sleep, depressed mood, anxiety and inflexible cognitive functioning; as well as a wide variety of medical and psychiatric conditions [213, 215–219].

ANS Control in Gut Inflammation–Relationships Between Central and Peripheral Nervous Systems in IBDs

The ANS maintains constant communication between the brain and the gut [220]. Evidence from animal and human studies has

revealed a set of physiological, behavioral, motivational, and cognitive changes accompanying activation of the immune system, such as malaise, fever, hyperalgesia, increased need to sleep, disturbed mood and impaired concentration and learning. Together these are known as the acute sickness response-a highly organised and evolved disease fighting strategy to increase survival [221–223]. Study of the sickness response is an important key to understanding the role of the brain in sickness and recovery, including intestinal inflammation. Further investigations into the mechanisms of the sickness response at the molecular level revealed that sickness-related changes are due to the effects of proinflammatory cytokines (IL-1; including IL-1α and IL-1β, IL-6 and TNF-α) on the brain [224, 225]. The gut environment fosters a broad network of enteric neurones, innervating the gut in close proximity to gut homing immune cells. This complex innervating network includes myenteric plexus that innervates longitudinal and circular smooth muscles in muscularis externae which is also the home for immune effector cells [226]. Submucosal plexus secretomotor neurons innervate goblet cells and enterocytes [226]. The afferent vasodilator neurones and sympathetic vasoconstrictive nerves, coat submucosal vasculature and regulate the function of these tissues in response to mechanical (stretch of the wall, mucosal layer damage) or chemical (bacterial products, toxins), stimuli [227, 228].

Inflammatory bowel diseases are associated with upregulation of the intestinal immune response with increased proinflammatory cytokines and chemokines during the active phase of the disease [3]. Clinical evidence has indicated a possible relationship between ANS function and inflammatory activities in IBDs. The ANS, together with the enteric nervous system (ENS) have important roles in gastrointestinal motility, secretion and mucosal immune response [229]. Furthermore, research in animal models of intestinal inflammation has addressed the role of ANS as an important modulator of inflammatory activities [205]. Such studies highlighted the position of the sympathetic and parasympathetic nervous system in intestinal inflammation, including altered ANS activity in UC patients [230, 231] and disparity in vagal tone in CD and IBS patients [232]. In the presence of gut inflammation or injury, peripherally released cytokines can influence the brain via hard-wired, fast-tracked pathways (from afferent nerves innervating the inflamed site) and via slower endocrine pathway (e.g. cytokines originating in the choroid plexus and circumventricular organs, and their volume transmission into the brain through blood brain barriers) [224, 233]. These two pathways act independently of each other [234]. Endocrine afferent transmission of inflammatory signaling to the brain is through a slower trail and by the production of molecular intermediates including prostaglandins in response to an increase in inflammatory cytokine levels. This pathway also activates the hypothalamus-pituitary-adrenal (HPA) axis, which in return releases anti-inflammatory and immunosuppressive proteins–the glucocorticoids. Neuroanatomical studies of gastrointestinal afferent neurons show that there are three neural pathways transmitting signals from the gut to the CNS including vagal afferent signals (vagal afferent fibers are densely concentrated in upper GI tract), pelvic afferent signals (mainly from the colorectal regions) and splanchnic afferents [235]. One fast tract afferent neural pathway is through sensory neurons of the vagus nerve innervating organs of the abdominal cavity that express receptors for proinflammatory cytokines. The vagus nerve (the body's longest nerve with 20% efferent and 80% afferent fibres) is a component of the neuro-immune axis through its efferent and afferent fibres. It is the chief constituent of the parasympathetic nervous system (PNS) and connects the CNS to major visceral organs (including lungs, heart, and gut), [220]. During intestinal inflammation and the release of proinflammatory cytokines, visceral information is transferred to the nucleus tractus solitarius (NTS) in the medulla oblongata in CNS either through activated vagal afferent nerves or through splanchnic and pelvic nerve afferents to the thoracolumbar and sacral spinal cord [220, 236, 237]. The brain's response to intestinal inflammation is translated into action potentials in the efferent vagus nerve which function to inhibit the production of proinflammatory cytokines [238]. This anti-inflammatory property of vagus nerve is through efferent cholinergic anti-inflammatory pathways. This circuit fundamentally includes the interaction between neurotransmitter acetylcholine and its alpha7 nicotinic acetylcholine receptor subunit expressed on monocytes, macrophages and other cytokine producing cells [239], restraining cytokine release, reducing production of TNF-α by macrophages (by blocking α7nAChR) to attenuate inflammation [240–245] and preventing tissue damage in the gut [246–248].

The sympathetic division enables both the stimulation of proinflammatory mediators (in the acute phase of inflammation) and anti-inflammatory properties (in the chronic phase of inflammation) [249, 250]. The sympathetic nervous system (SNS) and its neurotransmitters-the catecholamines, modulate GI movement, reduce intestinal motility, control secretion in GI tract (through its postganglionic sympathetic innervations), induce vasoregulation [250–252] and potentiate inflammatory cascades in the presence of immunogenic stimuli [232, 253–256]. Sympathetic innervating axons are in close proximity to GALT homing T cells, B cells, macrophages and mast cells [257]. Mast cells homing in intestinal mucosa are important mediators in inflammatory processes by releasing a variety of cytokines and chemokines, inducing intestinal hyper-permeability and activating inflammatory cascades [249, 250, 258, 259]. In the presence of an immunogenic stimulus, the sympathetic signaling pathways act to upregulate the host immune response against the stimuli through activating immune and enteroendocrine cells, and this is frequently accompanied by heightening visceral sensation, [230, 260–262]. Some clinical studies have suggested that the presence of such systemic inflammatory disorder leads to the development of autonomic dysfunction in CD and UC patients [263–267]. In addition, it is possible that consistent sympathetic hyperactivity in the presence of chronic inflammatory disorders such IBDs initiate autonomic dysfunction as seen in chronic depression or chronic heart diseases [250, 268]. Such findings broadly support the interplay between the intestinal immune system and inflammatory cell activity with the autonomic and

enteric nervous system and the CNS [269]. Despite mixed results from several clinical studies in regard to a possible causal role for autonomic dysfunction in the disease aetiology [230, 267], all have shown evidence of autonomic impairment in chronic inflammatory disorders [205].

Measures of Autonomic Reactivity

Experimental studies enhanced our understanding on how physiological stimuli, affect autonomic regulation and dynamically regulate heart rate through vagal and sympathetic efferent nerves [270, 271]. In healthy subjects the electrical activity of the sinoatrial node located at the posterior wall of the right atrium initiates each beat of the heart. Due to the unstable membrane potential of the myocytes located in this region, action potentials are generated periodically at a fairly constant frequency. This relatively constant frequency-generated by the autorhythmicity of the sinoatrial node-is modulated by many factors that add variability to the heart rate signal at different frequencies. These frequencies are affected by temperature regulations, endocrine systems, cardiac sympathetic and parasympathetic nerve activity, and respiratory rhythm (Task force of European Society of Cardiology and The North American Society of Pacing and Electrophysiology, 1999). Physical activity and/or experiencing stressful events involve a shift toward sympathetic dominance and a concomitant increase in the heart rate. A number of cardiac autonomic measures such as the time-to-recovery of resting heart rate after stress and certain parameters of beat-to-beat heart rate variability (HRV) are considered valid scientific tools to quantify autonomic balance and by inference the inhibitory influence of prefrontal cortical circuits, through parasympathetic (vagal) pathways, on sympathetic nerve activity [272]. This is supported by evidence from clinical studies which has consistently identified low HRV as an indicator of diminished parasympathetic control and a marker for increased risk of morbidity and mortality [273, 274]. Such evidence implicates autonomic dysfunction as specified by decreased HRV together with increased levels of systemic inflammatory markers (CRP and IL-6) [275] in heightened risk of cardiovascular morbidity [276]. Additionally low HRV has been linked to psychosocial variables and perceived stress [277] as well as clinical depression [278] and chronic fatigue syndrome [201]. In patients with IBDs, assessments of beat-to-beat HRV during autonomic arousal in response to stressors has similarly suggested impaired autonomic functioning [229, 279]. Evidence from examining HRV and autonomic reactivity in IBD patients in remission has suggested autonomic recovery indicated by a swing toward stronger parasympathetic responses, lower systemic inflammatory activity (CRP) and sympathetic withdrawal [229, 280].

Psychosocial Factors
Introduction

An organism's response to environmental stressors–which may constitute real or perceived threats to body integrity and homeostasis–consists of activating a complex range of pathways, involving the endocrine, nervous, and immune systems [281]. The short-term fight-or-flight stress response enables survival by shifting to sympathetic dominance, which stimulates the neuro-endocrine and cardiovascular systems to favor endurance and increase survival [282]. This response includes physiological and behavioural changes such as increased awareness, heightened arousal, increased cardiovascular tone, increased respiratory rate, improved analgesia [283], immune activation and inhibition of vegetative tasks (such as feeding, digestion, reproduction) [63]. Inappropriate activation of the stress response, which is common to many psychological disorders such as anxiety, has been linked to a wide array of pathological conditions including autoimmune disease, hypertension and affective disorders, [63]. A body of literature has been published on possible associations between psychological state and disease activities in chronic inflammatory diseases such as IBD; so far, however, there has been little consensus on whether psychological distress should be considered a cause or effect in IBDs or both.

Inflammatory Bowel Diseases are Associated with Clinically Significant Psychological Manifestations

There have been many studies in IBD documenting an association between the onset of IBD with recent stressful life events and suggested any perceived psychological distress even not related to disease activity can also influence the course of the disease [65, 284, 285]. Such studies also examined the effects by the disease on patients' psychological state. IBDs are chronic debilitating disorders which may affect many aspects of the sufferer's life and can add to the psychological burden including high levels of perceived stress [286], negative mood and depression [287] and anxiety compared to the healthy population [288]. The prevalence estimate of both depression and anxiety were higher in IBD patients -even among patients in remission-than what was expected in general population [289–291]. Studies have shown associations between symptoms of depression and anxiety with more severe IBD symptoms, more episodes of relapse in IBD patients [292], and higher rates of hospitalisation [293]. On the other hand, observed co-morbidities of high anxiety and depression irrespective to the disease itself in IBD patients have raised the idea of a causal relationship between these two conditions and IBD symptoms [294]. Two national representative population-based Canadian surveys [295] reported that IBD patients have 3 times higher depression rates than the healthy population. The same results were identified in the study by Mikocka-Walus et al, especially in patients during active phases of the disease [296]. A systematic review on primary studies examining depression and anxiety in IBD patients between years 1967–2014 [73] suggested that nearly one-fifth of IBD patients have shown depressive symptoms and approximately one-third were experienced anxiety symptoms. Such systematic reviews similarly suggested that patients with active disease had significantly higher prevalence of depression (40.7%) than those in remission (16.5%) [290, 291] and anxiety symptoms were more prevalent in active disease than those who were in remission. Furthermore, anxiety and depression were more common in CD patients compared to those with UC [291].

However, there were mixed and conflicting results to determine whether depression and anxiety developed before or after onset of IBD [297, 298]. Such mixed results might have been

simply driven from the methological differences in study design with limitted controlling for confounder or biases including recall biase (retrospective Vs prospective study design, short term assesment Vs longitudinal assessment, one off data collection Vs time series examination), models for data collection (qualitataive Vs quantitative) and/or study population/cohort under observation (which may not have been completely representative) i.e. some studies examined both CD and UC patients in one IBD cohort and some examined the psychological states in IBD patients irrespective of the disease activity (active Vs remission) or disaese phenotype/behavior. Also, such variations might have been caused by differences in healthcare system, community awareness of the disease, differences in lifestyle, environmental factors, access to medication in the countries studied.

Many IBD symptoms may be due to stress-induced changes in gastrointestinal function, immune regulation [297] and by affecting the composition of gut microbiota as a result of reducing the microbial diversity and increasing the ratio of inflammation-promoting bacteria [253]. Evidence from studies of experimental stress in animal models of colitis supports the association between psychological distress and IBD disease activity; showing a model of psychoneuroimmunology in interaction between immune function, nervous system and gut microbiota composition and function [253]. Studies also show that psychological distress and IBD disease activity consistently predict lower quality of life measures [296, 299]. IBD patients who show symptoms of anxiety and depression have reported lower quality of life [300, 301] and the disease course is more sever in those IBD patients with depression [64]. It is important to clinically identify psychological distress to ensure that patients are receiving IBD-specific psychological support as part of a patient focused model of care.

Neuropsychological State and IBDs-a Rapid Response

The difficulty in examining the relationship between psychological states and the course of IBDs is mainly related to whether the psychological distress is the product of the IBDs as a chronic inflammatory and debilitating disorder or a predisposing and contributing risk factor for the onset and/or maintenance of the diseases. Both the autonomic nervous system and HPA axis are actively involved in the inflammatory responses in human [302]. Moreover, both can be stimulated by psychological and physical stimuli, which in turn suggests that neuropsychological states can affect the progress and intensity of chronic inflammatory disorders such as IBD. This also indicates that the up- or down-regulation of the HPA axis and ANS response during chronic inflammation may both affect the physiological response to stress.

As both psychological factors and autonomic nervous system are integrated and can influence patients' effective adjustment to the course of the disease, both need to be considered in IBDs [303]. ANS regulates bidirectional neural cross talk including via autonomic afferents to the CNS, which in turn adjusts efferent signaling of the ANS [304, 305]. Neural circuits in higher brain regions including the prefrontal cortex, the hippocampus, and the amygdala can also control these efferent regions [289, 306] and modulate gut function, in addition to influencing the emotions,

cognition and behaviour [307, 308]. Although the literature suggests the presence of an autonomic dysfunction in IBD patients, the extent of such autonomic dysfunction depends on patients' coping strategies and emotional states. The mechanism of this dysfunction is not very well understood [303].

Hormonal Response and Psychological Stress

Psychological distress can threaten homeostasis therefore homeostasis is re-established by various physiological and behavioral adaptive responses. Neuroendocrine hormones have major roles in the regulation of both basal homeostasis and responses to threats and are involved in the pathogenesis of diseases. The stress response is mediated centrally, as well as in peripheral tissue through peripheral mediating systems. While rapidly responding ANS mediators of the stress response have been outlined above, the principal sites that modulate hormonal stress responses are the hypothalamus (the paraventricular nucleus-PVN), the anterior lobe of pituitary gland, and the adrenal gland (the hypothalamic-pituitary-adrenal axis), as well as sympathetic adreno-medullary circuits, causing the release of adrenaline [309, 310]. The principal regulator of the HPA axis is corticotropin releasing factor (CRF), secreted by the hypothalamus in response to environmental stimuli and stress. The hypophysial portal vessels transfer CRF to the anterior pituitary gland and induce the release of adrenocorticotropic hormone (ACTH) after binding to CRF receptors [311]. ACTH reaches the adrenal cortex by the systemic circulation and stimulates the synthesis and release of glucocorticoids. Glucocorticoids are a major subclass of steroid hormones and downstream effectors for HPA axis that modulate the body's physiological changes [300]. Glucocorticoids regulate metabolic, cardiovascular, immune, and behavioural processes [283]. These processes are accountable for adaptive changes, but depend on the type, period, and intensity of the stimuli as well as extent of the activation of HPA axis, with excessive or inadequate activation possibly engendering a pathologic impact on the body and lead to a host of behavioral and somatic pathological conditions [312]. Psychological and emotional stress can affect the sensory and secretory function of digestive system [313] and may alter the cholinergic nervous system, function of intestinal mucosal mast cells and subsequently increases in intestinal permeability [314], which is commonly observed in the active phase of IBD.

Conclusion

In the last few decades, there has been a surge of interest in studying the factors affecting the onset and severity of IBDs. Although the etiology of the IBDs is not very well understood, it is increasingly clear that multiple factors including genetic, environmental, psychological, autonomic, immunological, and gut microbiota interact and contribute to the disease manifestations and their persistence.

Genetic studies of IBD have highlighted the role of genetic susceptibility and its likely co-dependence with other mediators such as environmental, immune, and microbial factors. Recently, a considerable body of literature has accumulated relating to the effect of psychological state and IBDs, indicating higher level of depression, stress and anxiety experienced by sufferers especially in the active phase of the disease. Psychological distress is an

inseparable element of chronic disorders; hence there is still a need of comprehensive qualitative and quantitative research to investigate the causality of psychological factors and IBD activity. IBDs are characterised by prolonged immune activation in the gut in association with a breakdown in regulatory constraint, and dysbiosis. It is not clear though, if immune activation is a product of dysbiosis or the loss of tolerance in innate and adaptive immunity in the inflamed gut environment. Although a shift in the microbial diversity and IBD phenotype has been addressed in many clinical and experimental studies, thus far no evidence exists to confirm causation.

The significant association between a maladaptive autonomic reactivity with the onset and manifestations of some chronic disorders has suggested possible links between the ANS and IBDs disease activity. It is important that research examining a role for vulnerabilities and individual differences of IBD patients incorporates longitudinal assessments of biological and psychological factors and their temporal trajectory (including in remission and relapse) with the aim of characterising the risk factors and interdependence of these major factors in the course of the disease. Previous published studies were limited in the number of risk factors examined, or they lacked longitudinal analysis of such factors contributing to IBD disease activity [61, 291, 315, 316].

AUTHOR CONTRIBUTIONS

Author distribution: The main and corresponding author was responsible for conducting the research and investigation process, specifically performing review of multidisciplinary papers in main clinical areas of inflammation, neuropsychology, immunology, microbiology, psychology, and their relationships with chronic inflammatory diseases such as IBD. Contributing authors played major responsibilities of supervision, academic guidance, review, validation and editing the literature review.

FUNDING

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

REFERENCES

1. Andrews, JMIBD what Is it and Does Psyche Have Anything to Do with it? In: *Psychological Aspects of Inflammatory Bowel Disease*. Oxford, United Kingdom: A biopsychosocial approach(2014).

2. Yang, Y, Owyang, C, and Wu, GD East Meets West: The Increasing Incidence of Inflammatory Bowel Disease in Asia as a Paradigm for Environmental Effects on the Pathogenesis of Immune-Mediated Disease. *Gastroenterol* (2016). 151(6):e1–e5. doi:10.1053/j.gastro.2016.10.034

3. Xavier, RJ, and Podolsky, DK Unravelling the Pathogenesis of Inflammatory Bowel Disease. *Nature* (2007). 448(7152):427. doi:10.1038/nature06005

4. Molodecky, NA, Soon, IS, Rabi, DM, Ghali, WA, Ferris, M, Chernoff, G, et al. Increasing Incidence and Prevalence of the Inflammatory Bowel Diseases with Time, Based on Systematic Review. *Gastroenterol* (2012). 142(1):46–54. e42. doi:10.1053/j.gastro.2011.10.001

5. Knowles, SR, and Mikocka-Walus, AA. *Psychological Aspects of Inflammatory Bowel Disease: A Biopsychosocial Approach*. Paignton, United Kingdom: Routledge (2014).

6. Thia, KT, Loftus, Jr, EV, Sandborn, WJ, and Yang, S-K An Update on the Epidemiology of Inflammatory Bowel Disease in Asia. *Am J Gastroenterol* (2008). 103(12):3167–82. doi:10.1111/j.1572-0241.2008.02158.x

7. Ng, SC, Tang, W, Ching, JY, Wong, M, Chow, CM, Hui, AJ, et al. Incidence and Phenotype of Inflammatory Bowel Disease Based on Results from the Asia-Pacific Crohn's and Colitis Epidemiology Study. *Gastroenterol* (2013). 145(1):158–65. doi:10.1053/j.gastro.2013.04.007

8. Studd, C, Cameron, G, Beswick, L, Knight, R, Hair, C, McNeil, J, et al. Never Underestimate Inflammatory Bowel Disease: High Prevalence Rates and Confirmation of High Incidence Rates in Australia. *J Gastroenterol Hepatol* (2016). 31(1):81–6. doi:10.1111/jgh.13050

9. Vegh, Z, Burisch, J, Pedersen, N, Kaimakliotis, I, Duricova, D, Bortlik, M, et al. Incidence and Initial Disease Course of Inflammatory Bowel Diseases in 2011 in Europe and Australia: Results of the 2011 ECCO-EpiCom Inception Cohort. *J Crohn's Colitis* (2014). 8(11):1506–15. doi:10.1016/j.crohns.2014.06.004

10. Wilson, J, Hair, C, Knight, R, Catto-Smith, A, Bell, S, Kamm, M, et al. High Incidence of Inflammatory Bowel Disease in Australia: A Prospective Population-Based Australian Incidence Study. *Inflamm Bowel Dis* (2010). 16(9):1550–6. doi:10.1002/ibd.21209

11. Podolsky, DK Inflammatory Bowel Disease. *N Engl J Med* (1991). 325(14): 1008–16. doi:10.1056/nejm199110033251406

12. Baumgart, DC, and Sandborn, WJ Inflammatory Bowel Disease: Clinical Aspects and Established and Evolving Therapies. *The Lancet* (2007). 369(9573):1641–57. doi:10.1016/s0140-6736(07)60751-x

13. Baumgart, M, Dogan, B, Rishniw, M, Weitzman, G, Bosworth, B, Yantiss, R, et al. Culture Independent Analysis of Ileal Mucosa Reveals a Selective Increase in Invasive Escherichia coli of Novel Phylogeny Relative to Depletion of Clostridiales in Crohn's Disease Involving the Ileum. *Isme J* (2007). 1(5):403. doi:10.1038/ismej.2007.52

14. Strober, W, Fuss, I, and Mannon, P The Fundamental Basis of Inflammatory Bowel Disease. *J Clin Invest* (2007). 117(3):514–21. doi:10.1172/jci30587

15. Tysk, C, Lindberg, E, Järnerot, G, and Floderus-Myrhed, B Ulcerative Colitis and Crohn's Disease in an Unselected Population of Monozygotic and Dizygotic Twins. A Study of Heritability and the Influence of Smoking. *Gut* (1988). 29(7):990–6. doi:10.1136/gut.29.7.990

16. Mayberry, JF, Rhodes, J, and Newcombe, RG Familial Prevalence of Inflammatory Bowel Disease in Relatives of Patients with Crohn's Disease. *Bmj* (1980). 280(6207):84. doi:10.1136/bmj.280.6207.84

17. Monsén, U, Broström, O, Nordenvall, B, Sörstad, J, and Hellers, G Prevalence of Inflammatory Bowel Disease Among Relatives of Patients with Ulcerative Colitis. *Scand J Gastroenterol* (1987). 22(2):214–8. doi:10.3109/00365528708991882

18. Brant, SR Update on the Heritability of Inflammatory Bowel Disease: the Importance of Twin Studies. *Inflamm Bowel Dis* (2011). 17(1):1–5. doi:10.1002/ibd.21385

19. Edwards, SL, Beesley, J, French, JD, and Dunning, AM Beyond GWASs: Illuminating the Dark Road from Association to Function. *Am J Hum Genet* (2013). 93(5):779–97. doi:10.1016/j.ajhg.2013.10.012

20. Ye, BD, and McGovern, DPB Genetic Variation in IBD: Progress, Clues to Pathogenesis and Possible Clinical Utility. *Expert Rev Clin Immunol* (2016). 12(10):1091–107. doi:10.1080/1744666x.2016.1184972

21. Cleynen, I, and Vermeire, S The Genetic Architecture of Inflammatory Bowel Disease: Past, Present and Future. *Curr Opin Gastroenterol* (2015). 31(6):456–63. doi:10.1097/MOG.0000000000000215

22. Liu, JZ, van Sommeren, S, van Sommeren, S, Huang, H, Ng, SC, Alberts, R, et al. Association Analyses Identify 38 Susceptibility Loci for Inflammatory Bowel Disease and Highlight Shared Genetic Risk across Populations. *Nat Genet* (2015). 47(9):979–86. doi:10.1038/ng.3359

23. Zhernakova, A, Van Diemen, CC, and Wijmenga, C Detecting Shared Pathogenesis from the Shared Genetics of Immune-Related Diseases. *Nat Rev Genet* (2009). 10(1):43. doi:10.1038/nrg2489

24. Lees, CW, Barrett, JC, Parkes, M, and Satsangi, J New IBD Genetics: Common Pathways with Other Diseases. *Gut* (2011). 60(12):1739–53. doi:10.1136/gut.2009.199679

25. Ogura, Y, Bonen, DK, Inohara, N, Nicolae, DL, Chen, FF, Ramos, R, et al. A Frameshift Mutation in NOD2 Associated with Susceptibility to Crohn's Disease. *Nature* (2001). 411(6837):603–6. doi:10.1038/35079114

26. Loftus, EV, Silverstein, M, Sandborn, W, Tremaine, W, Harmsen, W, and Zinsmeister, A Ulcerative Colitis in Olmsted County, Minnesota, 1940-1993: Incidence, Prevalence, and Survival. *Gut* (2000). 46(3):336–43. doi:10.1136/gut.46.3.336

27. Loftus, EV, Jr, Silverstein, MD, Sandborn, WJ, Tremaine, WJ, Harmsen, WS, and Zinsmeister, AR Crohn's Disease in Olmsted County, Minnesota, 1940-1993: Incidence, Prevalence, and Survival. *Gastroenterol* (1998). 114(6):1161–8. doi:10.1016/s0016-5085(98)70421-4

28. Bernstein, CN, Rawsthorne, P, Cheang, M, and Blanchard, JF A Population-Based Case Control Study of Potential Risk Factors for IBD. *Am J Gastroenterol* (2006). 101(5):993–1002. doi:10.1111/j.1572-0241.2006.00381.x

29. Timm, S, Svanes, C, Janson, C, Sigsgaard, T, Johannessen, A, Gislason, T, et al. Place of Upbringing in Early Childhood as Related to Inflammatory Bowel Diseases in Adulthood: a Population-Based Cohort Study in Northern Europe. *Eur J Epidemiol* (2014). 29(6):429–37. doi:10.1007/s10654-014-9922-3

30. Bager, P, Simonsen, J, Nielsen, NM, and Frisch, M Cesarean Section and Offspring's Risk of Inflammatory Bowel Disease: A National Cohort Study. *Inflamm Bowel Dis* (2012). 18(5):857–62. doi:10.1002/ibd.21805

31. Barclay, AR, Russell, RK, Wilson, ML, Gilmour, WH, Satsangi, J, and Wilson, DC Systematic Review: the Role of Breastfeeding in the Development of Pediatric Inflammatory Bowel Disease. *J Pediatr* (2009). 155(3):421–6. doi:10.1016/j.jpeds.2009.03.017

32. Castiglione, F, Diaferia, M, Morace, F, Labianca, O, Meucci, C, Cuomo, A, et al. Risk Factors for Inflammatory Bowel Diseases According to the "hygiene Hypothesis": A Case-Control, Multi-Centre, Prospective Study in Southern Italy. *J Crohn's Colitis* (2012). 6(3):324–9. doi:10.1016/j.crohns.2011.09.003

33. Ng, SC, Tang, W, Leong, RW, Chen, M, Ko, Y, Studd, C, et al. Environmental Risk Factors in Inflammatory Bowel Disease: a Population-Based Case-Control Study in Asia-Pacific. *Gut* (2015). 64(7):1063–71. doi:10.1136/gutjnl-2014-307410

34. David, LA, Maurice, CF, Carmody, RN, Gootenberg, DB, Button, JE, Wolfe, BE, et al. Diet Rapidly and Reproducibly Alters the Human Gut Microbiome. *Nature* (2014). 505(7484):559–63. doi:10.1038/nature12820

35. Wu, GD, Chen, J, Hoffmann, C, Bittinger, K, Chen, Y-Y, Keilbaugh, SA, et al. Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes. *Science* (2011). 334(6052):105–8. doi:10.1126/science.1208344

36. Farzaei, M, Rahimi, R, and Abdollahi, M The Role of Dietary Polyphenols in the Management of Inflammatory Bowel Disease. *Cpb* (2015). 16(3):196–210. doi:10.2174/1389201016666150118131704

37. Hou, JK, Abraham, B, and El-Serag, H Dietary Intake and Risk of Developing Inflammatory Bowel Disease: a Systematic Review of the Literature. *Am J Gastroenterol* (2011). 106(4):563–73. doi:10.1038/ajg.2011.44

38. Olendzki, BC, Silverstein, TD, Persuitte, GM, Ma, Y, Baldwin, KR, and Cave, D An Anti-inflammatory Diet as Treatment for Inflammatory Bowel Disease: a Case Series Report. *Nutr J* (2014). 13(1):5. doi:10.1186/1475-2891-13-5

39. Persson, P-G, Ahlbom, A, and Hellers, Gr. Diet and Inflammatory Bowel Disease: a Case-Control Study. *Epidemiol* (1992). 3:47–52. doi:10.1097/00001648-199201000-00009

40. Mahid, SS, Minor, KS, Soto, RE, Hornung, CA, and Galandiuk, S Smoking and Inflammatory Bowel Disease: a Meta-Analysis. *Mayo Clin Proc* (2006). 81:1462. doi:10.4065/81.11.1462

41. Harries, AD, Baird, A, and Rhodes, J Non-smoking: a Feature of Ulcerative Colitis. *Bmj* (1982). 284(6317):706. doi:10.1136/bmj.284.6317.706

42. Higuchi, LM, Khalili, H, Chan, AT, Richter, JM, Bousvaros, A, and Fuchs, CS A Prospective Study of Cigarette Smoking and the Risk of Inflammatory Bowel Disease in Women. *Am J Gastroenterol* (2012). 107(9):1399. doi:10.1038/ajg.2012.196

43. Odes, HS, Fich, A, Reif, S, Halak, A, Lavy, A, Keter, D, et al. Effects of Current Cigarette Smoking on Clinical Course of Crohn's Disease and Ulcerative Colitis. *Dig Dis Sci* (2001). 46(8):1717–21. doi:10.1023/a:1010609722315

44. Cosnes, J Tobacco and IBD: Relevance in the Understanding of Disease Mechanisms and Clinical Practice. *Best Pract Res Clin Gastroenterol* (2004). 18(3):481–96. doi:10.1016/j.bpg.2003.12.003

45. Cosnes, J What Is the Link between the Use of Tobacco and IBD?. *Inflamm Bowel Dis* (2008). 14(Suppl. l_2):S14–S15. doi:10.1002/ibd.20555

46. Lakatos, PL, Szamosi, T, and Lakatos, L Smoking in Inflammatory Bowel Diseases: Good, Bad or Ugly? *Wjg* (2007). 13(46):6134. doi:10.3748/wjg.v13.i46.6134

47. Andersson, RE, Olaison, G, Tysk, C, and Ekbom, A Appendectomy and Protection against Ulcerative Colitis. *N Engl J Med* (2001). 344(11):808–14. doi:10.1056/nejm200103153441104

48. Andersson, RE, Olaison, G, Tysk, C, and Ekbom, A Appendectomy Is Followed by Increased Risk of Crohn's Disease. *Gastroenterol* (2003). 124(1):40–6. doi:10.1053/gast.2003.50021

49. Shaw, SY, Blanchard, JF, and Bernstein, CN Association between the Use of Antibiotics in the First Year of Life and Pediatric Inflammatory Bowel Disease. *Am J Gastroenterol* (2010). 105(12):2687–92. doi:10.1038/ajg.2010.398

50. Virta, L, Auvinen, A, Helenius, H, Huovinen, P, and Kolho, K-L Association of Repeated Exposure to Antibiotics with the Development of Pediatric Crohn's Disease--A Nationwide, Register-Based Finnish Case-Control Study. *Am J Epidemiol* (2012). 175(8):775–84. doi:10.1093/aje/kwr400

51. Rogler, G, and Vavricka, S Exposome in IBD: Recent Insights in Environmental Factors that Influence the Onset and Course of IBD. *Inflamm Bowel Dis* (2014). 21(2):400–8. doi:10.1097/MIB.0000000000000229

52. Koloski, NA, Bret, L, and Radford-Smith, G Hygiene Hypothesis in Inflammatory Bowel Disease: a Critical Review of the Literature. *Wjg* (2008). 14(2):165. doi:10.3748/wjg.14.165

53. Strachan, DP Hay Fever, Hygiene, and Household Size. *Bmj* (1989). 299(6710):1259. doi:10.1136/bmj.299.6710.1259

54. Saidel-Odes, L, and Odes, S Hygiene Hypothesis in Inflammatory Bowel Disease. *Ann Gastroenterol* (2014). 27(3):189. doi:10.3748/wjg.14.165

55. Bolíbar, I, Plaza, V, Llauger, M, Amado, E, Antón, PA, Espinosa, A, et al. Assessment of a Primary and Tertiary Care Integrated Management Model for Chronic Obstructive Pulmonary Disease. *BMC Public Health* (2009). 9(1):68. doi:10.1186/1471-2458-9-68

56. Cooper, CL, and Marshall, J Occupational Sources of Stress: A Review of the Literature Relating to Coronary Heart Disease and Mental Ill Health. In: *Managerial, Occupational and Organizational Stress Research*. Manchester, United Kingdom: Routledge (2018). p. 3–20.

57. Lloyd, CE Diabetes and Mental Health; the Problem of Co-morbidity. *Diabetic Med* (2010). 27(8):853–4. doi:10.1111/j.1464-5491.2010.03067.x

58. Orr, JG, Homer, T, Ternent, L, Newton, J, McNeil, CJ, Hudson, M, et al. Health Related Quality of Life in People with Advanced Chronic Liver Disease. *J Hepatol* (2014). 61(5):1158–65. doi:10.1016/j.jhep.2014.06.034

59. Rutledge, T, Redwine, LS, Linke, SE, and Mills, PJ A Meta-Analysis of Mental Health Treatments and Cardiac Rehabilitation for Improving Clinical Outcomes and Depression Among Patients with Coronary Heart Disease. *Psychosomatic Med* (2013). 75(4):335–49. doi:10.1097/psy.0b013e318291d798

60. Mikocka-Walus, AA, Turnbull, DA, Moulding, NT, Wilson, IG, Andrews, JM, and Holtmann, GJ Controversies Surrounding the Comorbidity of Depression and Anxiety in Inflammatory Bowel Disease Patients: a Literature Review. *Inflamm Bowel Dis* (2007). 13(2):225–34. doi:10.1002/ibd.20062

61. Gracie, DJ, Guthrie, EA, Hamlin, PJ, and Ford, AC Bi-directionality of Brain-Gut Interactions in Patients with Inflammatory Bowel Disease. *Gastroenterol* (2018). 154(6):1635–46. e1633. doi:10.1053/j.gastro.2018.01.027

62. Alexander, JK, DeVries, AC, Kigerl, KA, Dahlman, JM, and Popovich, PG Stress Exacerbates Neuropathic Pain via Glucocorticoid and NMDA Receptor Activation. *Brain Behav Immun* (2009). 23(6):851–60. doi:10.1016/j.bbi.2009.04.001

63. Sapolsky, RM, Romero, LM, and Munck, AU How Do Glucocorticoids Influence Stress Responses? Integrating Permissive, Suppressive, Stimulatory, and Preparative Actions. *Endocr Rev* (2000). 21(1):55–89. doi:10.1210/er.21.1.55

64. Graff, LA, Walker, JR, and Bernstein, CN Depression and Anxiety in Inflammatory Bowel Disease: a Review of Comorbidity and Management. *Inflamm Bowel Dis* (2009). 15(7):1105–18. doi:10.1002/ibd.20873

65. Panara, AJ, Yarur, AJ, Rieders, B, Proksell, S, Deshpande, AR, Abreu, MT, et al. The Incidence and Risk Factors for Developing Depression after Being Diagnosed with Inflammatory Bowel Disease: a Cohort Study. *Aliment Pharmacol Ther* (2014). 39(8):802–10. doi:10.1111/apt.12669

66. Ananthakrishnan, AN Environmental Triggers for Inflammatory Bowel Disease. *Curr Gastroenterol Rep* (2013b). 15(1):302. doi:10.1007/s11894-012-0302-4

67. Ananthakrishnan, AN Environmental Risk Factors for Inflammatory Bowel Disease. *Gastroenterol Hepatol (N Y)* (2013a). 9(6):367.

68. Ananthakrishnan, AN Epidemiology and Risk Factors for IBD. *Nat Rev Gastroenterol Hepatol* (2015). 12(4):205. doi:10.1038/nrgastro.2015.34

69. Sajadinejad, M, Asgari, K, Molavi, H, Kalantari, M, and Adibi, P Psychological Issues in Inflammatory Bowel Disease: an Overview. *Gastroenterol Res Pract* (2012). 106502. doi:10.1155/2012/106502

70. Froch, B, Zwolińska-Wcisło, M, Bętkowska-Korpała, B, and Mach, T The Dynamics of Emotional Reactions in Patients with Inflammatory Bowel Disease. *Gastroenterol Review/Przegląd Gastroenterologiczny* (2009). 4(3):141–6.

71. Kovács, Z, and Kovács, F Depressive and Anxiety Symptoms, Dysfunctional Attitudes and Social Aspects in Irritable Bowel Syndrome and Inflammatory Bowel Disease. *Int J Psychiatry Med* (2007). 37(3):245–55. doi:10.2190/pm.37.3.a

72. Mikocka-Walus, AA Treatment of Psychological Co-morbidities in Common Gastrointestinal and Hepatologic Disorders. *Wjgpt* (2010). 1(2):64. doi:10.4292/wjgpt.v1.i2.64

73. Neuendorf, R, Harding, A, Stello, N, Hanes, D, and Wahbeh, H Depression and Anxiety in Patients with Inflammatory Bowel Disease: A Systematic Review. *J psychosomatic Res* (2016). 87:70–80. doi:10.1016/j.jpsychores.2016.06.001

74. Crane, C, and Martin, M Social Learning, Affective State and Passive Coping in Irritable Bowel Syndrome and Inflammatory Bowel Disease. *Gen Hosp Psychiatry* (2004). 26(1):50–8. doi:10.1016/j.genhosppsych.2003.07.005

75. Guthrie, E, Jackson, J, Shaffer, J, Thompson, D, Tomenson, B, and Creed, F Psychological Disorder and Severity of Inflammatory Bowel Disease Predict Health-Related Quality of Life in Ulcerative Colitis and Crohn's Disease. *Am J Gastroenterol* (2002). 97(8):1994. doi:10.1111/j.1572-0241.2002.05842.x

76. Kurina, LM, Goldacre, M, Yeates, D, and Gill, L Depression and Anxiety in People with Inflammatory Bowel Disease. *J Epidemiol Community Health* (2001). 55(10):716–20. doi:10.1136/jech.55.10.716

77. Keefer, L, Keshavarzian, A, and Mutlu, E Reconsidering the Methodology of "Stress" Research in Inflammatory Bowel Disease. *J Crohn's Colitis* (2008). 2(3):193–201. doi:10.1016/j.crohns.2008.01.002

78. Kiank, C, Taché, Y, and Larauche, M Stress-related Modulation of Inflammation in Experimental Models of Bowel Disease and Post-infectious Irritable Bowel Syndrome: Role of Corticotropin-Releasing Factor Receptors. *Brain Behav Immun* (2010). 24(1):41–8. doi:10.1016/j.bbi.2009.08.006

79. Bayliss, WM, and Starling, EH The Movements and Innervation of the Small Intestine. *J Physiol* (1899). 24(2):99–143. doi:10.1113/jphysiol.1899.sp000752

80. Furness, JB The Enteric Nervous System: Normal Functions and Enteric Neuropathies. *Neurogastroenterol Motil* (2008). 20(s1):32–8. doi:10.1111/j.1365-2982.2008.01094.x

81. Mayer, EA Gut Feelings: the Emerging Biology of Gut-Brain Communication. *Nat Rev Neurosci* (2011). 12(8):453–66. doi:10.1038/nrn3071

82. Lyte, M, Vulchanova, L, and Brown, DR Stress at the Intestinal Surface: Catecholamines and Mucosa-Bacteria Interactions. *Cell Tissue Res* (2011). 343(1):23–32. doi:10.1007/s00441-010-1050-0

83. Pavlov, VA, and Tracey, KJ The Cholinergic Anti-inflammatory Pathway. *Brain Behav Immun* (2005). 19(6):493–9. doi:10.1016/j.bbi.2005.03.015

84. Goto, Y, Kurashima, Y, and Kiyono, H The Gut Microbiota and Inflammatory Bowel Disease. *Curr Opin Rheumatol* (2015). 27(4):388–96. doi:10.1097/bor.0000000000000192

85. Hold, GL, Smith, M, Grange, C, Watt, ER, El-Omar, EM, and Mukhopadhya, I Role of the Gut Microbiota in Inflammatory Bowel Disease Pathogenesis: what Have We Learnt in the Past 10 years? *Wjg* (2014). 20(5):1192. doi:10.3748/wjg.v20.i5.1192

86. Sheehan, D, Moran, C, and Shanahan, F The Microbiota in Inflammatory Bowel Disease. *J Gastroenterol* (2015). 50(5):495–507. doi:10.1007/s00535-015-1064-1

87. Bernstein, CN, and Forbes, JD Gut Microbiome in Inflammatory Bowel Disease and Other Chronic Immune-Mediated Inflammatory Diseases. *Inflamm Intest Dis* (2017). 2(2):116–23. doi:10.1159/000481401

88. Mackos, AR, Maltz, R, and Bailey, MT The Role of the Commensal Microbiota in Adaptive and Maladaptive Stressor-Induced Immunomodulation. *Horm Behav* (2017). 88:70–8. doi:10.1016/j.yhbeh.2016.10.006

89. Paun, A, Yau, C, and Danska, JS Immune Recognition and Response to the Intestinal Microbiome in Type 1 Diabetes. *J Autoimmun* (2016). 71:10–8. doi:10.1016/j.jaut.2016.02.004

90. Halfvarson, J, Brislawn, CJ, Lamendella, R, Vázquez-Baeza, Y, Walters, WA, Bramer, LM, et al. Dynamics of the Human Gut Microbiome in Inflammatory Bowel Disease. *Nat Microbiol* (2017). 2(5):1–7. doi:10.1038/nmicrobiol.2017.4

91. Kostic, AD, Xavier, RJ, and Gevers, D The Microbiome in Inflammatory Bowel Disease: Current Status and the Future Ahead. *Gastroenterol* (2014). 146(6):1489–99. doi:10.1053/j.gastro.2014.02.009

92. Wlodarska, M, Kostic, AD, and Xavier, RJ An Integrative View of Microbiome-Host Interactions in Inflammatory Bowel Diseases. *Cell Host & Microbe* (2015). 17(5):577–91. doi:10.1016/j.chom.2015.04.008

93. Strober, W, and Fuss, IJ Proinflammatory Cytokines in the Pathogenesis of Inflammatory Bowel Diseases. *Gastroenterol* (2011). 140(6):1756–67. e1751. doi:10.1053/j.gastro.2011.02.016

94. Mann, ER, and Li, X Intestinal Antigen-Presenting Cells in Mucosal Immune Homeostasis: Crosstalk between Dendritic Cells, Macrophages and B-Cells. *Wjg* (2014). 20(29):9653. doi:10.3748/wjg.v20.i29.9653

95. Murphy, K, and Weaver, C. *Janeway's Immunobiology*. New York, NY: Garland Science (2016).

96. Kmieć, Z, Cyman, M, and Ślebioda, TJ Cells of the Innate and Adaptive Immunity and Their Interactions in Inflammatory Bowel Disease. *Adv Med Sci* (2017). 62(1):1–16. doi:10.1016/j.advms.2016.09.001

97. Furrie, E, Macfarlane, S, Thomson, G, and Macfarlane, GT Toll-like Receptors-2, -3 and -4 Expression Patterns on Human Colon and Their Regulation by Mucosal-Associated Bacteria. *Immunol* (2005). 115(4):565–74. doi:10.1111/j.1365-2567.2005.02200.x

98. Lotz, M, Gütle, D, Walther, S, Ménard, S, Bogdan, C, and Hornef, MW Postnatal Acquisition of Endotoxin Tolerance in Intestinal Epithelial Cells. *J Exp Med* (2006). 203(4):973–84. doi:10.1084/jem.20050625

99. Aliprantis, AO, Yang, R-B, Mark, MR, Suggett, S, Devaux, B, Radolf, JD, et al. Cell Activation and Apoptosis by Bacterial Lipoproteins through Toll-like Receptor-2. *Science* (1999). 285(5428):736–9. doi:10.1126/science.285.5428.736

100. Schwandner, R, Dziarski, R, Wesche, H, Rothe, M, and Kirschning, CJ Peptidoglycan- and Lipoteichoic Acid-Induced Cell Activation Is Mediated by Toll-like Receptor 2. *J Biol Chem* (1999). 274(25):17406–9. doi:10.1074/jbc.274.25.17406

101. Hemmi, H, Takeuchi, O, Kawai, T, Kaisho, T, Sato, S, Sanjo, H, et al. A Toll-like Receptor Recognizes Bacterial DNA. *Nature* (2000). 408(6813):740–5. doi:10.1038/35047123

102. Kumar, A, Wu, H, Collier-Hyams, LS, Hansen, JM, Li, T, Yamoah, K, et al. Commensal Bacteria Modulate Cullin-dependent Signaling via Generation of Reactive Oxygen Species. *Embo J* (2007). 26(21):4457–66. doi:10.1038/sj.emboj.7601867

103. Cario, E, and Podolsky, DK Differential Alteration in Intestinal Epithelial Cell Expression of Toll-like Receptor 3 (TLR3) and TLR4 in Inflammatory Bowel Disease. *Infect Immun* (2000). 68(12):7010–7. doi:10.1128/iai.68.12.7010-7017.2000

104. Otte, J-M, Cario, E, and Podolsky, DK Mechanisms of Cross Hyporesponsiveness to Toll-like Receptor Bacterial Ligands in Intestinal Epithelial Cells☆. *Gastroenterol* (2004). 126(4):1054–70. doi:10.1053/j.gastro.2004.01.007

105. Khan, MA, Ma, C, Knodler, LA, Valdez, Y, Rosenberger, CM, Deng, W, et al. Toll-like Receptor 4 Contributes to Colitis Development but Not to Host Defense during Citrobacter Rodentium Infection in Mice. *Iai* (2006). 74(5):2522–36. doi:10.1128/iai.74.5.2522-2536.2006

106. Lavelle, EC, Murphy, C, O'Neill, LAJ, and Creagh, EM The Role of TLRs, NLRs, and RLRs in Mucosal Innate Immunity and Homeostasis. *Mucosal Immunol* (2010). 3(1):17–28. doi:10.1038/mi.2009.124

107. Lee, J, Mo, J-H, Katakura, K, Alkalay, I, Rucker, AN, Liu, Y-T, et al. Maintenance of Colonic Homeostasis by Distinctive Apical TLR9 Signalling in Intestinal Epithelial Cells. *Nat Cel Biol* (2006). 8(12):1327–36. doi:10.1038/ncb1500

108. Abreu, MT, Fukata, M, and Arditi, M TLR Signaling in the Gut in Health and Disease. *J Immunol* (2005). 174(8):4453–60. doi:10.4049/jimmunol.174.8.4453

109. Kobayashi, KS, Chamaillard, M, Ogura, Y, Henegariu, O, Inohara, N, Nunez, G, et al. Nod2-dependent Regulation of Innate and Adaptive Immunity in the Intestinal Tract. *Science* (2005). 307(5710):731–4. doi:10.1126/science.1104911

110. May, MJ, and Ghosh, S Signal Transduction through NF-Kb. *Immunol Today* (1998). 19(2):80–8. doi:10.1016/s0167-5699(97)01197-3

111. Hoesel, B, and Schmid, JA The Complexity of NF-Kb Signaling in Inflammation and Cancer. *Mol Cancer* (2013). 12(1):86. doi:10.1186/1476-4598-12-86

112. Hayden, MS, and Ghosh, S Shared Principles in NF-Kb Signaling. *Cell* (2008). 132(3):344–62. doi:10.1016/j.cell.2008.01.020

113. Reboldi, A, and Cyster, JG Peyer's Patches: Organizing B-Cell Responses at the Intestinal Frontier. *Immunol Rev* (2016). 271(1):230–45. doi:10.1111/imr.12400

114. Macpherson, AJ, and Harris, NL Interactions between Commensal Intestinal Bacteria and the Immune System. *Nat Rev Immunol* (2004). 4(6):478–85. doi:10.1038/nri1373

115. Stecher, B, Robbiani, R, Walker, AW, Westendorf, AM, Barthel, M, Kremer, M, et al. Salmonella enterica Serovar Typhimurium Exploits Inflammation to Compete with the Intestinal Microbiota. *Plos Biol* (2007). 5(10):e244. doi:10.1371/journal.pbio.0050244

116. Rescigno, M, Urbano, M, Valzasina, B, Francolini, M, Rotta, G, Bonasio, R, et al. Dendritic Cells Express Tight Junction Proteins and Penetrate Gut Epithelial Monolayers to Sample Bacteria. *Nat Immunol* (2001). 2(4):361–7. doi:10.1038/86373

117. Niess, JH, Brand, S, Gu, X, Landsman, L, Jung, S, McCormick, BA, et al. CX3CR1-mediated Dendritic Cell Access to the Intestinal Lumen and Bacterial Clearance. *Science* (2005). 307(5707):254–8. doi:10.1126/science.1102901

118. Maloy, KJ, and Powrie, F Intestinal Homeostasis and its Breakdown in Inflammatory Bowel Disease. *Nature* (2011). 474(7351):298. doi:10.1038/nature10208

119. Wendelsdorf, K, Bassaganya-Riera, J, Hontecillas, R, and Eubank, S Model of Colonic Inflammation: Immune Modulatory Mechanisms in Inflammatory Bowel Disease. *J Theor Biol* (2010). 264(4):1225–39. doi:10.1016/j.jtbi.2010.03.027

120. Neurath, MF Cytokines in Inflammatory Bowel Disease. *Nat Rev Immunol* (2014). 14(5):329–42. doi:10.1038/nri3661

121. Sanchez-Muñoz, F, Dominguez-Lopez, A, and Yamamoto-Furusho, JK Role of Cytokines in Inflammatory Bowel Disease. *Wjg* (2008). 14(27):4280. doi:10.3748/wjg.14.4280

122. Caza, T, and Landas, S Functional and Phenotypic Plasticity of CD4(+) T Cell Subsets. *Biomed Res Int* (2015). 2015:521957. doi:10.1155/2015/521957

123. Kobayashi, T, Okamoto, S, Hisamatsu, T, Kamada, N, Chinen, H, Saito, R, et al. IL23 Differentially Regulates the Th1/Th17 Balance in Ulcerative Colitis and Crohn's Disease. *Gut* (2008). 57(12):1682–9. doi:10.1136/gut.2007.135053

124. Singh, RP, Hasan, S, Sharma, S, Nagra, S, Yamaguchi, DT, Wong, DTW, et al. Th17 Cells in Inflammation and Autoimmunity. *Autoimmun Rev* (2014). 13(12):1174–81. doi:10.1016/j.autrev.2014.08.019

125. Ivanov, II, Frutos, Rd. L, Manel, N, Yoshinaga, K, Rifkin, DB, Sartor, RB, et al. Specific Microbiota Direct the Differentiation of IL-17-producing T-Helper Cells in the Mucosa of the Small Intestine. *Cell Host & Microbe* (2008). 4(4):337–49. doi:10.1016/j.chom.2008.09.009

126. Ishikawa, H, Tanaka, K, Maeda, Y, Aiba, Y, Hata, A, Tsuji, NM, et al. Effect of Intestinal Microbiota on the Induction of Regulatory CD25+ CD4+ T Cells. *Clin Exp Immunol* (2008). 153(1):127–35. doi:10.1111/j.1365-2249.2008.03668.x

127. Braunstein, J, Qiao, L, Autschbach, F, Schürmann, G, and Meuer, S T Cells of the Human Intestinal Lamina Propria Are High Producers of Interleukin-10. *Gut* (1997). 41(2):215–20. doi:10.1136/gut.41.2.215

128. Monteleone, G, Kumberova, A, Croft, NM, McKenzie, C, Steer, HW, and MacDonald, TT Blocking Smad7 Restores TGF-B1 Signaling in Chronic Inflammatory Bowel Disease. *J Clin Invest* (2001). 108(4):601. doi:10.1172/jci12821

129. Thompson, C, and Powrie, F Regulatory T Cells. *Curr Opin Pharmacol* (2004). 4(4):408–14. doi:10.1016/j.coph.2004.05.001

130. Vignali, DAA, Collison, LW, and Workman, CJ How Regulatory T Cells Work. *Nat Rev Immunol* (2008). 8(7):523–32. doi:10.1038/nri2343

131. Mähler, M, and Leiter, EH Genetic and Environmental Context Determines the Course of Colitis Developing in IL-10-Deficient Mice. *Inflamm Bowel Dis* (2002). 8(5):347–55. doi:10.1097/00054725-200209000-00006

132. Sellon, RK, Tonkonogy, S, Schultz, M, Dieleman, LA, Grenther, W, Balish, E, et al. Resident Enteric Bacteria Are Necessary for Development of Spontaneous Colitis and Immune System Activation in Interleukin-10-Deficient Mice. *Infect Immun* (1998). 66(11):5224–31. doi:10.1128/iai.66.11.5224-5231.1998

133. Guarner, F, and Malagelada, J-R Gut Flora in Health and Disease. *The Lancet* (2003). 361(9356):512–9. doi:10.1016/s0140-6736(03)12489-0

134. Duchmann, R, Kaiser, I, Hermann, E, Mayet, W, Ewe, K, and Meyer zum Büschenfelde, KH Tolerance Exists towards Resident Intestinal Flora but Is Broken in Active Inflammatory Bowel Disease (IBD). *Clin Exp Immunol* (1995). 102(3):448–55. doi:10.1111/j.1365-2249.1995.tb03836.x

135. Garside, P, Mowat, AM, and Khoruts, A Oral Tolerance in Disease. *Gut* (1999). 44(1):137–42. doi:10.1136/gut.44.1.137

136. Round, JL, and Mazmanian, SK The Gut Microbiota Shapes Intestinal Immune Responses during Health and Disease. *Nat Rev Immunol* (2009). 9(5):313–23. doi:10.1038/nri2515

137. Dickinson, RJ, O'connor, HJ, Pinder, I, Hamilton, I, Johnston, D, and Axon, AT Double Blind Controlled Trial of Oral Vancomycin as Adjunctive Treatment in Acute Exacerbations of Idiopathic Colitis. *Gut* (1985). 26(12):1380–4. doi:10.1136/gut.26.12.1380

138. Khan, KJ, Ullman, TA, Ford, AC, Abreu, MT, Abadir, A, Marshall, JK, et al. Antibiotic Therapy in Inflammatory Bowel Disease: a Systematic Review and Meta-Analysis. *Am J Gastroenterol* (2011). 106(4):661. doi:10.1038/ajg.2011.72

139. Sartor, RB Therapeutic Manipulation of the Enteric Microflora in Inflammatory Bowel Diseases: Antibiotics, Probiotics, and Prebiotics. *Gastroenterol* (2004). 126(6):1620–33. doi:10.1053/j.gastro.2004.03.024

140. Mennigen, R, Heptner, B, Senninger, N, and Rijcken, E. *Temporary Fecal Diversion in the Management of Colorectal and Perianal Crohn's Disease*. Muenster, Germany: Gastroenterology research and practice (2015).

141. Singh, S, Ding, NS, Mathis, KL, Dulai, PS, Farrell, AM, Pemberton, JH, et al. Systematic Review with Meta-Analysis: Faecal Diversion for Management of Perianal Crohn's Disease. *Aliment Pharmacol Ther* (2015). 42(7):783–92. doi:10.1111/apt.13356

142. Yamamoto, T, Allan, RN, and Keighley, MRB Effect of Fecal Diversion Alone on Perianal Crohn's Disease. *World J Surg* (2000). 24(10):1258–63. doi:10.1007/s002680010250

143. Tannock, GW Exploring the Relationships between Intestinal Microflora and Inflammatory Conditions of the Human Bowel and Spine. *Antonie Van Leeuwenhoek* (2002). 81(1):529–35. doi:10.1023/a:1020517603993

144. Ley, RE, Peterson, DA, and Gordon, JI Ecological and Evolutionary Forces Shaping Microbial Diversity in the Human Intestine. *Cell* (2006a). 124(4):837–48. doi:10.1016/j.cell.2006.02.017

145. Cani, PD, and Delzenne, NM Gut Microflora as a Target for Energy and Metabolic Homeostasis. *Curr Opin Clin Nutr Metab Care* (2007). 10(6):729–34. doi:10.1097/mco.0b013e3282efdebb

146. Dave, M, Higgins, PD, Middha, S, and Rioux, KP The Human Gut Microbiome: Current Knowledge, Challenges, and Future Directions. *Translational Res* (2012). 160(4):246–57. doi:10.1016/j.trsl.2012.05.003

147. Ley, RE, Turnbaugh, PJ, Klein, S, and Gordon, JI Human Gut Microbes Associated with Obesity. *Nature* (2006b). 444(7122):1022. doi:10.1038/4441022a

148. Turnbaugh, PJ, Ley, RE, Hamady, M, Fraser-Liggett, CM, Knight, R, and Gordon, JI The Human Microbiome Project. *Nature* (2007). 449(7164):804. doi:10.1038/nature06244

149. Qin, J, Li, R, Li, R, Raes, J, Arumugam, M, Burgdorf, KS, et al. A Human Gut Microbial Gene Catalogue Established by Metagenomic Sequencing. *Nature* (2010). 464(7285):59. doi:10.1038/nature08821

150. Faith, JJ, Guruge, JL, Charbonneau, M, Subramanian, S, Seedorf, H, Goodman, AL, et al. The Long-Term Stability of the Human Gut Microbiota. *Science* (2013). 341(6141):1237439. doi:10.1126/science.1237439

151. Rajilić-Stojanović, M, Smidt, H, and De Vos, WM Diversity of the Human Gastrointestinal Tract Microbiota Revisited. *Environ Microbiol* (2007). 9(9):2125–36. doi:10.1111/j.1462-2920.2007.01369.x

152. Choung, RS, Ruff, KC, Malhotra, A, Herrick, L, Locke, GR, Harmsen, WS, et al. Clinical Predictors of Small Intestinal Bacterial Overgrowth by Duodenal Aspirate Culture. *Aliment Pharmacol Ther* (2011). 33(9):1059–67. doi:10.1111/j.1365-2036.2011.04625.x

153. Gillilland, MG, Young, VB, and Huffnagle, GB Gastrointestinal Microbial Ecology with Perspectives on Health and Disease. In: *Physiology of the Gastrointestinal Tract*. Fifth Edition. Elsevier (2012). p. 1119–34.

154. Sartor, RB, and Mazmanian, SK Intestinal Microbes in Inflammatory Bowel Diseases. *Am J Gastroenterol Suppl* (2012). 1(1):15. doi:10.1038/ajgsup.2012.4

155. Hao, WL, and Lee, YK Microflora of the Gastrointestinal Tract: a Review. *Methods Mol Biol* (2004). 268:491–502. doi:10.1385/1-59259-766-1:491

156. Blaser, MJ, and Kirschner, D The Equilibria that Allow Bacterial Persistence in Human Hosts. *Nature* (2007). 449(7164):843–9. doi:10.1038/nature06198

157. Miyazawa, E, Iwabuchi, A, and Yoshida, T Phytate Breakdown and Apparent Absorption of Phosphorus, Calcium and Magnesium in Germfree and Conventionalized Rats. *Nutr Res* (1996). 16(4):603–13. doi:10.1016/0271-5317(96)00038-3

158. Bindels, LB, Dewulf, EM, and Delzenne, NM GPR43/FFA2: Physiopathological Relevance and Therapeutic Prospects. *Trends Pharmacological Sciences* (2013). 34(4):226–32. doi:10.1016/j.tips.2013.02.002

159. Flint, HJ, Scott, KP, Louis, P, and Duncan, SH The Role of the Gut Microbiota in Nutrition and Health. *Nat Rev Gastroenterol Hepatol* (2012). 9(10):577–89. doi:10.1038/nrgastro.2012.156

160. Gordon, JI, Hooper, LV, McNevin, MS, Wong, M, and Bry, L Epithelial Cell Growth and Differentiation. III. Promoting Diversity in the Intestine: Conversations between the Microflora, Epithelium, and Diffuse GALT. *Am J Physiology-Gastrointestinal Liver Physiol* (1997). 273(3):G565–G570. doi:10.1152/ajpgi.1997.273.3.g565

161. Pomare, EW, Branch, WJ, and Cummings, JH Carbohydrate Fermentation in the Human Colon and its Relation to Acetate Concentrations in Venous Blood. *J Clin Invest* (1985). 75(5):1448. doi:10.1172/jci111847

162. Karaki, S-i, Tazoe, H, Hayashi, H, Kashiwabara, H, Tooyama, K, Suzuki, Y, et al. Expression of the Short-Chain Fatty Acid Receptor, GPR43, in the Human Colon. *J Mol Hist* (2008). 39(2):135–42. doi:10.1007/s10735-007-9145-y

163. Sleeth, ML, Thompson, EL, Ford, HE, Zac-Varghese, SEK, and Frost, G Free Fatty Acid Receptor 2 and Nutrient Sensing: a Proposed Role for Fibre, Fermentable Carbohydrates and Short-Chain Fatty Acids in Appetite

164. Hamer, HM, Jonkers, D, Venema, K, Vanhoutvin, S, Troost, FJ, and Brummer, RJ Review Article: the Role of Butyrate on Colonic Function. *Aliment Pharmacol Ther* (2008). 27(2):104–19. doi:10.1111/j.1365-2036.2007.03562.x

165. Barko, PC, McMichael, MA, Swanson, KS, and Williams, DA The Gastrointestinal Microbiome: A Review. *J Vet Intern Med* (2017). 32(1):9–25. doi:10.1111/jvim.14875

166. Gallo, A, Passaro, G, Gasbarrini, A, Landolfi, R, and Montalto, M Modulation of Microbiota as Treatment for Intestinal Inflammatory Disorders: An Uptodate. *Wjg* (2016). 22(32):7186. doi:10.3748/wjg.v22.i32.7186

167. Shanahan, F Probiotics and Inflammatory Bowel Disease: Is There a Scientific Rationale?. *Inflamm Bowel Dis* (2000). 6(2):107–15. doi:10.1097/00054725-200005000-00007

168. Teitelbaum, JH, and Walker, WA Nutritionalimpact Ofpre-Andprobiotics Asprotectivegastrointestinalorganisms. *Annu Rev Nutr* (2002). 22(1):107–38. doi:10.1146/annurev.nutr.22.110901.145412

169. Giaffer, MH, Holdsworth, CD, and Duerden, BI The Assessment of Faecal Flora in Patients with Inflammatory Bowel Disease by a Simplified Bacteriological Technique. *J Med Microbiol* (1991). 35(4):238–43. doi:10.1099/00222615-35-4-238

170. Scanlan, PD, Shanahan, F, O'Mahony, C, and Marchesi, JR Culture-independent Analyses of Temporal Variation of the Dominant Fecal Microbiota and Targeted Bacterial Subgroups in Crohn's Disease. *J Clin Microbiol* (2006). 44(11):3980–8. doi:10.1128/jcm.00312-06

171. Seksik, P, Rigottier-Gois, L, Gramet, G, Sutren, M, Pochart, P, Marteau, P, et al. Alterations of the Dominant Faecal Bacterial Groups in Patients with Crohn's Disease of the Colon. *Gut* (2003). 52(2):237–42. doi:10.1136/gut.52.2.237

172. Stahl, DA, Lane, DJ, Olsen, GJ, and Pace, NR Analysis of Hydrothermal Vent-Associated Symbionts by Ribosomal RNA Sequences. *Science* (1984). 224(4647):409–11. doi:10.1126/science.224.4647.409

173. Handelsman, J Metagenomics: Application of Genomics to Uncultured Microorganisms. *Mmbr* (2004). 68(4):669–85. doi:10.1128/mmbr.68.4.669-685.2004

174. Pace, NR A Molecular View of Microbial Diversity and the Biosphere. *Science* (1997). 276:734–40. doi:10.1126/science.276.5313.734

175. Stein, JL, Marsh, TL, Wu, KY, Shizuya, H, and DeLong, EF Characterization of Uncultivated Prokaryotes: Isolation and Analysis of a 40-Kilobase-Pair Genome Fragment from a Planktonic Marine Archaeon. *J Bacteriol* (1996). 178(3):591–9. doi:10.1128/jb.178.3.591-599.1996

176. Fox, GE, Magrum, LJ, Balch, WE, Wolfe, RS, and Woese, CR Classification of Methanogenic Bacteria by 16S Ribosomal RNA Characterization. *Proc Natl Acad Sci* (1977). 74(10):4537–41. doi:10.1073/pnas.74.10.4537

177. Eckburg, PB, and Relman, DA The Role of Microbes in Crohn's Disease. *Clin Infect Dis* (2007). 44(2):256–62. doi:10.1086/510385

178. Frank, DN, St. Amand, AL, Feldman, RA, Boedeker, EC, Harpaz, N, and Pace, NR Molecular-phylogenetic Characterization of Microbial Community Imbalances in Human Inflammatory Bowel Diseases. *Proc Natl Acad Sci* (2007). 104(34):13780–5. doi:10.1073/pnas.0706625104

179. Goodrich, JK, Waters, JL, Poole, AC, Sutter, JL, Koren, O, Blekhman, R, et al. Human Genetics Shape the Gut Microbiome. *Cell* (2014). 159(4):789–99. doi:10.1016/j.cell.2014.09.053

180. Zhernakova, A, Kurilshikov, A, Bonder, MJ, Tigchelaar, EF, Schirmer, M, Vatanen, T, et al. Population-based Metagenomics Analysis Reveals Markers for Gut Microbiome Composition and Diversity. *Science* (2016). 352(6285):565–9. doi:10.1126/science.aad3369

181. Franzosa, EA, Huang, K, Meadow, JF, Gevers, D, Lemon, KP, Bohannan, BJM, et al. Identifying Personal Microbiomes Using Metagenomic Codes. *Proc Natl Acad Sci USA* (2015). 112(22):E2930–E2938. doi:10.1073/pnas.1423854112

182. Turnbaugh, PJ, Hamady, M, Yatsunenko, T, Cantarel, BL, Duncan, A, Ley, RE, et al. A Core Gut Microbiome in Obese and Lean Twins. *Nature* (2009). 457(7228):480. doi:10.1038/nature07540

183. Yatsunenko, T, Rey, FE, Manary, MJ, Trehan, I, Dominguez-Bello, MG, Contreras, M, et al. Human Gut Microbiome Viewed across Age and Geography. *Nature* (2012). 486(7402):222. doi:10.1038/nature11053

184. Ursell, LK, Clemente, JC, Rideout, JR, Gevers, D, Caporaso, JG, and Knight, R The Interpersonal and Intrapersonal Diversity of Human-Associated

Microbiota in Key Body Sites. *J Allergy Clin Immunol* (2012). 129(5):1204–8. doi:10.1016/j.jaci.2012.03.010

185. Ley, RE, Lozupone, CA, Hamady, M, Knight, R, and Gordon, JI Worlds within Worlds: Evolution of the Vertebrate Gut Microbiota. *Nat Rev Microbiol* (2008). 6(10):776. doi:10.1038/nrmicro1978

186. Palmer, C, Bik, EM, DiGiulio, DB, Relman, DA, and Brown, PO Development of the Human Infant Intestinal Microbiota. *Plos Biol* (2007). 5(7):e177. doi:10.1371/journal.pbio.0050177

187. Eckburg, PB, Bik, EM, Bernstein, CN, Purdom, E, Dethlefsen, L, Sargent, M, et al. Diversity of the Human Intestinal Microbial Flora. *Science* (2005). 308(5728):1635–8. doi:10.1126/science.1110591

188. Peterson, DA, Frank, DN, Pace, NR, and Gordon, JI Metagenomic Approaches for Defining the Pathogenesis of Inflammatory Bowel Diseases. *Cell Host & Microbe* (2008). 3(6):417–27. doi:10.1016/j.chom.2008.05.001

189. De Souza, HSP, and Fiocchi, C Immunopathogenesis of IBD: Current State of the Art. *Nat Rev Gastroenterol Hepatol* (2016). 13(1):13–27. doi:10.1038/nrgastro.2015.186

190. Mombaerts, P, Mizoguchi, E, Grusby, MJ, Glimcher, LH, Bhan, AK, and Tonegawa, S Spontaneous Development of Inflammatory Bowel Disease in T Cell Receptor Mutant Mice. *Cell* (1993). 75(2):275–82. doi:10.1016/0092-8674(93)80069-q

191. Darfeuille-Michaud, A, Boudeau, J, Bulois, P, Neut, C, Glasser, A-L, Barnich, N, et al. High Prevalence of Adherent-Invasive Escherichia coli Associated with Ileal Mucosa in Crohn's Disease. *Gastroenterol* (2004). 127(2):412–21. doi:10.1053/j.gastro.2004.04.061

192. Machiels, K, Joossens, M, Sabino, J, De Preter, V, Arijs, I, Eeckhaut, V, et al. A Decrease of the Butyrate-Producing Species Roseburia Hominis and Faecalibacterium Prausnitzii Defines Dysbiosis in Patients with Ulcerative Colitis. *Gut* (2013). 63(8):1275–83. doi:10.1136/gutjnl-2013-304833

193. Lupp, C, Robertson, ML, Wickham, ME, Sekirov, I, Champion, OL, Gaynor, EC, et al. Host-mediated Inflammation Disrupts the Intestinal Microbiota and Promotes the Overgrowth of Enterobacteriaceae. *Cell Host & Microbe* (2007). 2(2):119–29. doi:10.1016/j.chom.2007.06.010

194. Ohkusa, T, Sato, N, Ogihara, T, Morita, K, Ogawa, M, and Okayasu, I Fusobacterium Varium Localized in the Colonic Mucosa of Patients with Ulcerative Colitis Stimulates Species-specific Antibody. *J Gastroenterol Hepatol* (2002). 17(8):849–53. doi:10.1046/j.1440-1746.2002.02834.x

195. Geboes, K, Ectors, N, D'Haens, G, and Rutgeerts, P Is Ileoscopy with Biopsy Worthwhile in Patients Presenting with Symptoms of Inflammatory Bowel Disease? *Am J Gastroenterol* (1998). 93(2):201–6. doi:10.1111/j.1572-0241.1998.00201.x

196. Thompson-Chagoyán, OC, Maldonado, J, and Gil, A Aetiology of Inflammatory Bowel Disease (IBD): Role of Intestinal Microbiota and Gut-Associated Lymphoid Tissue Immune Response. *Clin Nutr* (2005). 24(3):339–52. doi:10.1016/j.clnu.2005.02.009

197. Carol, M, Borruel, N, Antolin, M, Llopis, M, Casellas, F, Guarner, F, et al. Modulation of Apoptosis in Intestinal Lymphocytes by a Probiotic Bacteria in Crohn's Disease. *J Leukoc Biol* (2006). 79(5):917–22. doi:10.1189/jlb.0405188

198. Llopis, M, Antolin, M, Carol, M, Borruel, N, Casellas, F, Martinez, C, et al. Lactobacillus Casei Downregulates Commensals' Inflammatory Signals in Crohn's Disease Mucosa. *Inflamm Bowel Dis* (2009). 15(2):275–83. doi:10.1002/ibd.20736

199. Taurog, JD, Richardson, JA, Croft, JT, Simmons, WA, Zhou, M, Fernández-Sueiro, JL, et al. The Germfree State Prevents Development of Gut and Joint Inflammatory Disease in HLA-B27 Transgenic Rats. *J Exp Med* (1994). 180(6):2359–64. doi:10.1084/jem.180.6.2359

200. Andersson, U, and Tracey, KJ Reflex Principles of Immunological Homeostasis. *Annu Rev Immunol* (2012). 30:313. doi:10.1146/annurev-immunol-020711-075015

201. Beaumont, A, Burton, AR, Lemon, J, Bennett, BK, Lloyd, A, and Vollmer-Conna, U Reduced Cardiac Vagal Modulation Impacts on Cognitive Performance in Chronic Fatigue Syndrome. *PloS one* (2012a). 7(11):e49518. doi:10.1371/journal.pone.0049518

202. Kadota, Y, Cooper, G, Burton, AR, Lemon, J, Schall, U, Lloyd, A, et al. Autonomic Hyper-Vigilance in Post-infective Fatigue Syndrome. *Biol Psychol* (2010). 85(1):97–103. doi:10.1016/j.biopsycho.2010.05.009

203. Joho, S, and Inoue, H [Autonomic Nervous System and Ischemic Heart Disease]. *Nippon Rinsho* (2003). 61 Suppl 5:903.

204. Agelink, MW, Boz, C, Ullrich, H, and Andrich, J Relationship between Major Depression and Heart Rate variabilityClinical Consequences and Implications for Antidepressive Treatment. *Psychiatry Res* (2002). 113(1-2):139–49. doi:10.1016/s0165-1781(02)00225-1

205. Boissé, L, Chisholm, SP, Lukewich, MK, and Lomax, AE Clinical and Experimental Evidence of Sympathetic Neural Dysfunction during Inflammatory Bowel Disease. *Clin Exp Pharmacol Physiol* (2009). 36(10):1026–33. doi:10.1111/j.1440-1681.2009.05242.x

206. Bonaz, B, Picq, C, Sinniger, V, Mayol, JF, and Clarençon, D Vagus Nerve Stimulation: from Epilepsy to the Cholinergic Anti-inflammatory Pathway. *Neurogastroenterology Motil* (2013). 25(3):208–21. doi:10.1111/nmo.12076

207. Vuilleumier, P How Brains Beware: Neural Mechanisms of Emotional Attention. *Trends Cognitive Sciences* (2005). 9(12):585–94. doi:10.1016/j.tics.2005.10.011

208. Craig, AD How Do You Feel? Interoception: the Sense of the Physiological Condition of the Body. *Nat Rev Neurosci* (2002). 3(8):655. doi:10.1038/nrn894

209. Taylor, CT, and Keely, SJ The Autonomic Nervous System and Inflammatory Bowel Disease. *Auton Neurosci* (2007). 133(1):104–14. doi:10.1016/j.autneu.2006.11.005

210. Williams, EK, Chang, RB, Strochlic, DE, Umans, BD, Lowell, BB, and Liberles, SD Sensory Neurons that Detect Stretch and Nutrients in the Digestive System. *Cell* (2016). 166:209. doi:10.1016/j.cell.2016.05.011

211. Craig, A Interoception: the Sense of the Physiological Condition of the Body. *Curr Opin Neurobiol* (2003). 13(4):500–5. doi:10.1016/s0959-4388(03)00090-4

212. LeDoux, J (1996). *The Emotional Brain: The Mysterious Underpinnings of Emotional Life*. Simon & Schuster New York.

213. Thayer, JF, and Brosschot, JF Psychosomatics and Psychopathology: Looking up and Down from the Brain. *Psychoneuroendocrinol* (2005). 30(10):1050–8. doi:10.1016/j.psyn.euen.2005.04.014

214. Amat, J, Baratta, MV, Paul, E, Bland, ST, Watkins, LR, and Maier, SF Medial Prefrontal Cortex Determines How Stressor Controllability Affects Behavior and Dorsal Raphe Nucleus. *Nat Neurosci* (2005). 8(3):365. doi:10.1038/nn1399

215. Thayer, JF, Hansen, AL, Saus-Rose, E, and Johnsen, BH Heart Rate Variability, Prefrontal Neural Function, and Cognitive Performance: the Neurovisceral Integration Perspective on Self-Regulation, Adaptation, and Health. *Ann Behav Med* (2009). 37(2):141–53. doi:10.1007/s12160-009-9101-z

216. Frijda, NH The Laws of Emotion. *Am Psychol* (1988). 43(5):349. doi:10.1037/0003-066x.43.5.349

217. McEwen, BS, and Seeman, T Protective and Damaging Effects of Mediators of Stress: Elaborating and Testing the Concepts of Allostasis and Allostatic Load. *Ann N Y Acad Sci* (1999). 896(1):30–47. doi:10.1111/j.1749-6632.1999.tb08103.x

218. Thayer, JF, and Friedman, BH. *The Heart of Anxiety: A Dynamical Systems Approach*. The (non) expression of emotions in health and disease (1997). p. 39–49.

219. Thayer, JF, and Lane, RD A Model of Neurovisceral Integration in Emotion Regulation and Dysregulation. *J affective Disord* (2000). 61(3):201–16. doi:10.1016/s0165-0327(00)00338-4

220. Bonaz, BL, and Bernstein, CN Brain-gut Interactions in Inflammatory Bowel Disease. *Gastroenterol* (2013). 144(1):36–49. doi:10.1053/j.gastro.2012.10.003

221. Hart, BL Biological Basis of the Behavior of Sick Animals. *Neurosci Biobehavioral Rev* (1988). 12(2):123–37. doi:10.1016/s0149-7634(88)80004-6

222. Maier, SF Bi-directional Immune-Brain Communication: Implications for Understanding Stress, Pain, and Cognition. *Brain Behav Immun* (2003). 17(2):69–85. doi:10.1016/s0889-1591(03)00032-1

223. Vollmer-Conna, U Acute Sickness Behaviour: an Immune System-To-Brain Communication?. *Psychol Med* (2001). 31(5):761–7. doi:10.1017/s0033291701003841

224. Banks, WA, Farr, SA, and Morley, JE Entry of Blood-Borne Cytokines into the Central Nervous System: Effects on Cognitive Processes. *Neuroimmunomodulation* (2002). 10(6):319–27. doi:10.1159/000071472

225. van Dam, A-M, Brouns, M, Louisse, S, and Berkenbosch, F Appearance of Interleukin-1 in Macrophages and in Ramified Microglia in the Brain of

Endotoxin-Treated Rats: a Pathway for the Induction of Non-specific Symptoms of Sickness? *Brain Res* (1992). 588(2):291–6. doi:10.1016/0006-8993(92)91588-6

226. Vanner, S, and Surprenant, A Neural Reflexes Controlling Intestinal Microcirculation. *Am J Physiology-Gastrointestinal Liver Physiol* (1996). 271(2):G223–G230. doi:10.1152/ajpgi.1996.271.2.g223

227. Bertrand, PP The Cornucopia of Intestinal Chemosensory Transduction. *Front Neurosci* (2009). 3:48. doi:10.3389/neuro.21.003.2009

228. Spencer, NJ, and Smith, TK Mechanosensory S-Neurons rather Than AH-Neurons Appear to Generate a Rhythmic Motor Pattern in guinea-pig Distal Colon. *J Physiol* (2004). 558(2):577–96. doi:10.1113/jphysiol.2004.063586

229. Mouzas, IA, Pallis, AG, Kochiadakis, GE, Marketou, M, Chlouverakis, GI, Mellisas, J, et al. Autonomic Imbalance during the Day in Patients with Inflammatory Bowel Disease in Remission. Evidence from Spectral Analysis of Heart Rate Variability over 24 hours. *Dig Liver Dis* (2002). 34(11):775–80. doi:10.1016/s1590-8658(02)80070-6

230. Ganguli, S, Kamath, M, Redmond, K, Chen, Y, Irvine, E, Collins, S, et al. A Comparison of Autonomic Function in Patients with Inflammatory Bowel Disease and in Healthy Controls. *Neurogastroenterology Motil* (2007). 19(12): 961–7. doi:10.1111/j.1365-2982.2007.00987.x

231. Maunder, RG, Greenberg, GR, Nolan, RP, Lancee, WJ, Steinhart, AH, and Hunter, JJ Autonomic Response to Standardized Stress Predicts Subsequent Disease Activity in Ulcerative Colitis. *Eur J Gastroenterol Hepatol* (2006). 18(4):413–20. doi:10.1097/00042737-200604000-00016

232. Pellissier, S, Dantzer, C, Mondillon, L, Trocme, C, Gauchez, A-S, Ducros, V, et al. Relationship between Vagal Tone, Cortisol, TNF-Alpha, Epinephrine and Negative Affects in Crohn's Disease and Irritable Bowel Syndrome. *PloS one* (2014). 9(9):e105328. doi:10.1371/journal.pone.0105328

233. Dantzer, R Cytokine-induced Sickness Behavior: where Do We Stand?. *Brain Behav Immun* (2001). 15(1):7–24. doi:10.1006/brbi.2000.0613

234. Konsman, JP, Parnet, P, and Dantzer, R Cytokine-induced Sickness Behaviour: Mechanisms and Implications. *Trends Neurosciences* (2002). 25(3):154–9. doi:10.1016/s0166-2236(00)02088-9

235. Berthoud, HR, Blackshaw, LA, Brookes, SJH, and Grundy, D Neuroanatomy of Extrinsic Afferents Supplying the Gastrointestinal Tract. *Neurogastroenterol Motil* (2004). 16(s1):28–33. doi:10.1111/j.1743-3150.2004.00471.x

236. Dantzer, R, Konsman, J-P, Bluthé, R-M, and Kelley, KW Neural and Humoral Pathways of Communication from the Immune System to the Brain: Parallel or Convergent?. *Auton Neurosci* (2000). 85(1-3):60–5. doi:10.1016/s1566-0702(00)00220-4

237. Ek, M, Kurosawa, M, Lundeberg, T, and Ericsson, A Activation of Vagal Afferents after Intravenous Injection of Interleukin-1β: Role of Endogenous Prostaglandins. *J Neurosci* (1998). 18(22):9471–9. doi:10.1523/jneurosci.18-22-09471.1998

238. Huston, JM, Ochani, M, Rosas-Ballina, M, Liao, H, Ochani, K, Pavlov, VA, et al. Splenectomy Inactivates the Cholinergic Antiinflammatory Pathway during Lethal Endotoxemia and Polymicrobial Sepsis. *J Exp Med* (2006). 203(7):1623–8. doi:10.1084/jem.20052362

239. Wang, H, Yu, M, Ochani, M, Amella, CA, Tanovic, M, Susarla, S, et al. Nicotinic Acetylcholine Receptor α7 Subunit Is an Essential Regulator of Inflammation. *Nature* (2003). 421(6921):384. doi:10.1038/nature01339

240. Bai, A, Guo, Y, and Lu, N The Effect of the Cholinergic Anti-inflammatory Pathway on Experimental Colitis. *Scand J Immunol* (2007). 66(5):538–45. doi:10.1111/j.1365-3083.2007.02011.x

241. Borovikova, LV, Ivanova, S, Nardi, D, Zhang, M, Yang, H, Ombrellino, M, et al. Role of Vagus Nerve Signaling in CNI-1493-Mediated Suppression of Acute Inflammation. *Auton Neurosci* (2000a). 85(1):141–7. doi:10.1016/s1566-0702(00)00233-2

242. de Jonge, WJ, van der Zanden, EP, The, FO, Bijlsma, MF, van Westerloo, DJ, Bennink, RJ, et al. Stimulation of the Vagus Nerve Attenuates Macrophage Activation by Activating the Jak2-STAT3 Signaling Pathway. *Nat Immunol* (2005). 6(8):844. doi:10.1038/ni1229

243. Meregnani, J, Clarençon, D, Vivier, M, Peinnequin, A, Mouret, C, Sinniger, V, et al. Anti-inflammatory Effect of Vagus Nerve Stimulation in a Rat Model of Inflammatory Bowel Disease. *Auton Neurosci* (2011). 160(1):82–9. doi:10.1016/j.autneu.2010.10.007

244. O'Mahony, C, van der Kleij, H, Bienenstock, J, Shanahan, F, and O'Mahony, L Loss of Vagal Anti-inflammatory Effect: In Vivo Visualization and Adoptive

Transfer. *Am J Physiology-Regulatory, Integr Comp Physiol* (2009). 297(4): R1118–R1126. doi:10.1152/ajpregu.90904.2008

245. Pavlov, VA, Wang, H, Czura, CJ, Friedman, SG, and Tracey, KJ The Cholinergic Anti-inflammatory Pathway: a Missing Link in Neuroimmunomodulation. *Mol Med* (2003). 9(5-8):125. doi:10.1007/bf03402177

246. Borovikova, LV, Ivanova, S, Zhang, M, Yang, H, Botchkina, GI, Watkins, LR, et al. Vagus Nerve Stimulation Attenuates the Systemic Inflammatory Response to Endotoxin. *Nature* (2000b). 405(6785):458. doi:10.1038/35013070

247. Ottani, A, Giuliani, D, Galantucci, M, Spaccapelo, L, Novellino, E, Grieco, P, et al. Melanocortins Counteract Inflammatory and Apoptotic Responses to Prolonged Myocardial Ischemia/reperfusion through a Vagus Nerve-Mediated Mechanism. *Eur J Pharmacol* (2010). 637(1-3):124–30. doi:10.1016/j.ejphar.2010.03.052

248. Van Westerloo, DJ, Giebelen, IA, Florquin, S, Daalhuisen, J, Bruno, MJ, de Vos, AF, et al. The Cholinergic Anti-inflammatory Pathway Regulates the Host Response during Septic Peritonitis. *J Infect Dis* (2005). 191(12):2138–48. doi:10.1086/430323

249. Pongratz, G, and Straub, RH The Sympathetic Nervous Response in Inflammation. *Arthritis Res Ther* (2014). 16(6):504. doi:10.1186/s13075-014-0504-2

250. Straub, RH, Wiest, R, Strauch, UG, Härle, P, and Schölmerich, J The Role of the Sympathetic Nervous System in Intestinal Inflammation. *Gut* (2006). 55(11):1640–9. doi:10.1136/gut.2006.091322

251. Furness, JB, Nguyen, TV, Nurgali, K, and Shimizu, Y The Enteric Nervous System and its Extrinsic Connections. *Textbook Gastroenterol* (1999). 15–39.

252. Lomax, a. e. Anti-inflammatory Effects of β3-adrenoceptors: the Burgeoning Field of Neurogastroimmunology. *Neurogastroenterology Motil* (2008). 20(9): 967–70. doi:10.1111/j.1365-2982.2008.01173.x

253. Gao, X, Cao, Q, Cheng, Y, Zhao, D, Wang, Z, Yang, H, et al. Chronic Stress Promotes Colitis by Disturbing the Gut Microbiota and Triggering Immune System Response. *Proc Natl Acad Sci USA* (2018). 115(13):E2960–E2969. doi:10.1073/pnas.1720696115

254. Grebe, KM, Takeda, K, Hickman, HD, Bailey, AM, Embry, AC, Bennink, JR, et al. Cutting Edge: Sympathetic Nervous System Increases Proinflammatory Cytokines and Exacerbates Influenza A Virus Pathogenesis. *J.I.* (2010). 184(2):540–4. doi:10.4049/jimmunol.0903395

255. Irwin, MR, and Cole, SW Reciprocal Regulation of the Neural and Innate Immune Systems. *Nat Rev Immunol* (2011). 11(9):625–32. doi:10.1038/nri3042

256. Spohn, SN, Bianco, F, Scott, RB, Keenan, CM, Linton, AA, O'Neill, CH, et al. Protective Actions of Epithelial 5-hydroxytryptamine 4 Receptors in Normal and Inflamed Colon. *Gastroenterol* (2016). 151(5):933–44. e933. doi:10.1053/j.gastro.2016.07.032

257. Stevens-Felten, SY, and Bellinger, DL Noradrenergic and Peptidergic Innervation of Lymphoid Organs. *Chem Immunol* (1997). 69:99–131. doi:10.1159/000058655

258. Bischoff, SC Physiological and Pathophysiological Functions of Intestinal Mast Cells. *Semin Immunopathol* (2009). 31:185. doi:10.1007/s00281-009-0165-4

259. Tache, Y, and Perdue, MH Role of Peripheral CRF Signalling Pathways in Stress-Related Alterations of Gut Motility and Mucosal Function. *Neurogastroenterol Motil* (2004). 16:137–42. doi:10.1111/j.1743-3150.2004.00490.x

260. McCAFFERTY, DM, Wallace, JL, and Sharkey, KA Effects of Chemical Sympathectomy and Sensory Nerve Ablation on Experimental Colitis in the Rat. *Am J Physiology-Gastrointestinal Liver Physiol* (1997). 272(2): G272–G280. doi:10.1152/ajpgi.1997.272.2.g272

261. Straub, RH, Grum, F, Strauch, U, Capellino, S, Bataille, F, Bleich, A, et al. Anti-inflammatory Role of Sympathetic Nerves in Chronic Intestinal Inflammation. *Gut* (2008). 57(7):911–21. doi:10.1136/gut.2007.125401

262. Straub, RH, Stebner, K, Härle, P, Kees, F, Falk, W, and Schölmerich, J Key Role of the Sympathetic Microenvironment for the Interplay of Tumour Necrosis Factor and Interleukin 6 in Normal but Not in Inflamed Mouse Colon Mucosa. *Gut* (2005). 54(8):1098–106. doi:10.1136/gut.2004.062877

263. Furlan, R, Ardizzone, S, Palazzolo, L, Rimoldi, A, Perego, F, Barbic, F, et al. Sympathetic Overactivity in Active Ulcerative Colitis: Effects of Clonidine.

Am J Physiology-Regulatory, Integr Comp Physiol (2006). 290(1):R224–R232. doi:10.1152/ajpregu.00442.2005

264. Lindgren, S, Lilja, B, Rosén, I, and Sundkvist, G Disturbed Autonomic Nerve Function in Patients with Crohn's Disease. *Scand J Gastroenterol* (1991). 26(4):361–6. doi:10.3109/00365529108996495

265. Lindgren, S, Stewenius, J, Sjölund, K, Lilja, B, and Sundkvist, G Autonomic Vagal Nerve Dysfunction in Patients with Ulcerative Colitis. *Scand J Gastroenterol* (1993). 28(7):638–42. doi:10.3109/00365529309096103

266. Maule, S, Pierangeli, G, Cevoli, S, Grimaldi, D, Gionchetti, P, Barbara, G, et al. Sympathetic Hyperactivity in Patients with Ulcerative Colitis. *Clin Auton Res* (2007). 17(4):217–20. doi:10.1007/s10286-007-0425-0

267. Ohlsson, B, Sundkvist, G, and Lindgren, S Subclinical Sympathetic Neuropathy Appears Early in the Course of Crohn's Disease. *BMC Gastroenterol* (2007). 7(1):33. doi:10.1186/1471-230x-7-33

268. Kishi, T Heart Failure as an Autonomic Nervous System Dysfunction. *J Cardiol* (2012). 59(2):117–22. doi:10.1016/j.jjcc.2011.12.006

269. Saunders, PR, Miceli, P, Vallance, BA, Wang, L, Pinto, S, Tougas, G, et al. Noradrenergic and Cholinergic Neural Pathways Mediate Stress-Induced Reactivation of Colitis in the Rat. *Auton Neurosci* (2006). 124(1):56–68. doi:10.1016/j.autneu.2005.12.002

270. Appel, ML, Berger, RD, Saul, JP, Smith, JM, and Cohen, RJ Beat to Beat Variability in Cardiovascular Variables: Noise or Music? *J Am Coll Cardiol* (1989). 14(5):1139–48. doi:10.1016/0735-1097(89)90408-7

271. Bernardi, L, Keller, F, Sanders, M, Reddy, PS, Griffith, B, Meno, F, et al. Respiratory Sinus Arrhythmia in the Denervated Human Heart. *J Appl Physiol* (1989). 67(4):1447–55. doi:10.1152/jappl.1989.67.4.1447

272. Goldberger, JJ, Le, FK, Lahiri, M, Kannankeril, PJ, Ng, J, and Kadish, AH Assessment of Parasympathetic Reactivation after Exercise. *Am J Physiology-Heart Circulatory Physiol* (2006). 290(6):H2446–H2452. doi:10.1152/ajpheart.01118.2005

273. Cole, CR, Foody, JM, Blackstone, EH, and Lauer, MS Heart Rate Recovery after Submaximal Exercise Testing as a Predictor of Mortality in a Cardiovascularly Healthy Cohort. *Ann Intern Med* (2000). 132(7):552–5. doi:10.7326/0003-4819-132-7-200004040-00007

274. Nishime, EO, Cole, CR, Blackstone, EH, Pashkow, FJ, and Lauer, MS Heart Rate Recovery and Treadmill Exercise Score as Predictors of Mortality in Patients Referred for Exercise ECG. *Jama* (2000). 284(11):1392–8. doi:10.1001/jama.284.11.1392

275. Sabatine, MS, Morrow, DA, Jablonski, KA, Rice, MM, Warnica, JW, Domanski, MJ, et al. Prognostic Significance of the Centers for Disease Control/American Heart Association High-Sensitivity C-Reactive Protein Cut Points for Cardiovascular and Other Outcomes in Patients with Stable Coronary Artery Disease. *Circulation* (2007). 115(12):1528–36. doi:10.1161/circulationaha.106.649939

276. Camm, AJ, Malik, M, Bigger, JT, Breithardt, G, Cerutti, S, Cohen, RJ, et al. Heart Rate Variability: Standards of Measurement, Physiological Interpretation and Clinical Use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* (1996). 93(5):1043–65. doi:10.1111/j.1542-474X.1996.tb00275.x

277. Patel, V, Giesebrecht, S, Burton, AR, Cvejic, E, Lemon, J, Hadzi-Pavlovic, D, et al. Reliability Revisited: Autonomic Responses in the Context of Everyday Well-Being. *Int J Cardiol* (2013). 166(3):743–5. doi:10.1016/j.ijcard.2012.09.177

278. Kemp, AH, Quintana, DS, Gray, MA, Felmingham, KL, Brown, K, and Gatt, JM Impact of Depression and Antidepressant Treatment on Heart Rate Variability: a Review and Meta-Analysis. *Biol Psychiatry* (2010). 67(11):1067–74. doi:10.1016/j.biopsych.2009.12.012

279. Frasure-Smith, N, Lespérance, F, Irwin, MR, Talajic, M, and Pollock, BG The Relationships Among Heart Rate Variability, Inflammatory Markers and Depression in Coronary Heart Disease Patients. *Brain Behav Immun* (2009). 23(8):1140–7. doi:10.1016/j.bbi.2009.07.005

280. Gunterberg, V, Simrén, M, Öhman, L, Friberg, P, Jones, MP, Van Oudenhove, L, et al. Autonomic Nervous System Function Predicts the Inflammatory Response over Three Years in Newly Diagnosed Ulcerative Colitis Patients. *Neurogastroenterol Motil* (2016). 28(11):1655–62. doi:10.1111/nmo.12865

281. Carrasco, GA, and Van de Kar, LD Neuroendocrine Pharmacology of Stress. *Eur J Pharmacol* (2003). 463(1):235–72. doi:10.1016/s0014-2999(03)01285-8

282. Dhabhar, FS A Hassle a Day May Keep the Pathogens Away: the Fight-Or-Flight Stress Response and the Augmentation of Immune Function. *Integr Comp Biol* (2009). 49(3):215–36. doi:10.1093/icb/icp045

283. Charmandari, E, Tsigos, C, and Chrousos, G Endocrinology of the Stress Response. *Annu Rev Physiol* (2005). 67:259–84. doi:10.1146/annurev.physiol.67.040403.120816

284. Lerebours, E, Gower-Rousseau, C, Merle, V, Brazier, F, Debeugny, S, Marti, R, et al. Stressful Life Events as a Risk Factor for Inflammatory Bowel Disease Onset: A Population-Based Case-Control Study. *Am J Gastroenterol* (2007). 102(1):122. doi:10.1111/j.1572-0241.2006.00931.x

285. Paull, A, and Hislop, IG Etiologic Factors in Ulcerative Colitis: Birth, Death and Symbolic Equivalents. *Int J Psychiatry Med* (1974). 5(1):57–64. doi:10.2190/kbck-2xjt-uwht-7c6a

286. Rogala, L, Miller, N, Graff, LA, Rawsthorne, P, Clara, I, Walker, JR, et al. Population-based Controlled Study of Social Support, Self-Perceived Stress, Activity and Work Issues, and Access to Health Care in Inflammatory Bowel Disease. *Inflamm Bowel Dis* (2008). 14(4):526–35. doi:10.1002/ibd.20353

287. Miehsler, W, Weichselberger, M, Öfferlbauer-Ernst, A, Dejaco, C, Reinisch, W, Vogelsang, H, et al. Which Patients with IBD Need Psychological Interventions? A Controlled Study. *Inflamm Bowel Dis* (2008). 14(9):1273–80. doi:10.1002/ibd.20462

288. Graff, LA, Vincent, N, Walker, JR, Clara, I, Carr, R, Ediger, J, et al. A Population-Based Study of Fatigue and Sleep Difficulties in Inflammatory Bowel Disease. *Inflamm Bowel Dis* (2010a). 17(9):1882–9. doi:10.1002/ibd.21580

289. Baxter, AJ, Scott, KM, Vos, T, and Whiteford, HA Global Prevalence of Anxiety Disorders: a Systematic Review and Meta-Regression. *Psychol Med* (2013). 43(5):897–910. doi:10.1017/s003329171200147x

290. Ferrari, AJ, Charlson, FJ, Norman, RE, Patten, SB, Freedman, G, Murray, CJ, et al. Burden of Depressive Disorders by Country, Sex, Age, and Year: Findings from the Global Burden of Disease Study 2010. *PLoS Med* (2013a). 10(11). doi:10.1371/journal.pmed.1001547

291. Mikocka-Walus, A, Knowles, SR, Keefer, L, and Graff, L Controversies Revisited. *Inflamm Bowel Dis* (2016a). 22(3):752–62. doi:10.1097/mib.0000000000000620

292. Mittermaier, C, Dejaco, C, Waldhoer, T, Oeerflbauer-Ernst, A, Miehsler, W, Beier, M, et al. Impact of Depressive Mood on Relapse in Patients with Inflammatory Bowel Disease: a Prospective 18-month Follow-Up Study. *Psychosomatic Med* (2004). 66(1):79–84. doi:10.1097/01.psy.0000106907.24881.f2

293. Van Langenberg, DR, Lange, K, Hetzel, DJ, Holtmann, GJ, and Andrews, JM Adverse Clinical Phenotype in Inflammatory Bowel Disease: a Cross Sectional Study Identifying Factors Potentially Amenable to Change. *J Gastroenterol Hepatol* (2010). 25(7):1250–8. doi:10.1111/j.1440-1746.2010.06302.x

294. Scott, KM, Bruffaerts, R, Tsang, A, Ormel, J, Alonso, J, Angermeyer, MC, et al. Depression-anxiety Relationships with Chronic Physical Conditions: Results from the World Mental Health Surveys. *J affective Disord* (2007). 103(1):113–20. doi:10.1016/j.jad.2007.01.015

295. Fuller-Thomson, E, and Sulman, J Depression and Inflammatory Bowel Disease: Findings from Two Nationally Representative Canadian Surveys. *Inflamm Bowel Dis* (2006). 12(8):697–707. doi:10.1097/00054725-200608000-00005

296. Mikocka-Walus, A, Pittet, V, Rossel, JB, von Känel, R, and Group, SICS Symptoms of Depression and Anxiety Are Independently Associated with Clinical Recurrence of Inflammatory Bowel Disease. *Clin Gastroenterol Hepatol* (2016b). 14(6):829–e1. e821. doi:10.1016/j.cgh.2015.12.045

297. Mawdsley, JE, and Rampton, D Psychological Stress in IBD: New Insights into Pathogenic and Therapeutic Implications. *Gut* (2005). 54(10):1481–91. doi:10.1136/gut.2005.064261

298. Mawdsley, JE, and Rampton, DS The Role of Psychological Stress in Inflammatory Bowel Disease. *Neuroimmunomodulation* (2006). 13(5-6):327–36. doi:10.1159/000104861

299. Graff, LA, Walker, JR, and Bernstein, CN It's Not Just about the Gut: Managing Depression and Anxiety in Inflammatory Bowel Disease. *Pract Gastroenterol* (2010b). 34(7):11–25.

300. Bamberger, CM, Schulte, HM, and Chrousos, GP Molecular Determinants of Glucocorticoid Receptor Function and Tissue Sensitivity to Glucocorticoids. *Endocr Rev* (1996). 17(3):245–61. doi:10.1210/edrv-17-3-245

301. Farrokhyar, F, Marshall, JK, Easterbrook, B, and Irvine, JE Functional Gastrointestinal Disorders and Mood Disorders in Patients with Inactive Inflammatory Bowel Disease: Prevalence and Impact on Health. *Inflamm Bowel Dis* (2006). 12(1):38–46. doi:10.1097/01.mib.0000195391.49762.89

302. Elenkov, IJ, and Chrousos, GP Stress Hormones, Proinflammatory and Antiinflammatory Cytokines, and Autoimmunity. *Ann N Y Acad Sci* (2002). 966(1):290–303. doi:10.1111/j.1749-6632.2002.tb04229.x

303. Pellissier, S, Dantzer, C, Canini, F, Mathieu, N, and Bonaz, B Psychological Adjustment and Autonomic Disturbances in Inflammatory Bowel Diseases and Irritable Bowel Syndrome. *Psychoneuroendocrinol* (2010). 35(5):653–62. doi:10.1016/j.psyneuen.2009.10.004

304. Mayer, EA, Naliboff, BD, and Craig, ADB Neuroimaging of the Brain-Gut axis: from Basic Understanding to Treatment of Functional GI Disorders. *Gastroenterol* (2006). 131(6):1925–42. doi:10.1053/j.gastro.2006.10.026

305. Koloski, NA, Jones, M, and Talley, NJ Evidence that Independent Gut-To-Brain and Brain-To-Gut Pathways Operate in the Irritable Bowel Syndrome and Functional Dyspepsia: a 1-year Population-Based Prospective Study. *Aliment Pharmacol Ther* (2006). 44(6):592–600. doi:10.1111/apt.13738

306. Saper, CB The Central Autonomic Nervous System: Conscious Visceral Perception and Autonomic Pattern Generation. *Annu Rev Neurosci* (2002). 25(1):433–69. doi:10.1146/annurev.neuro.25.032502.111311

307. Gillanders, S, Wild, M, Deighan, C, and Gillanders, D Emotion Regulation, Affect, Psychosocial Functioning, and Well-Being in Hemodialysis Patients. *Am J Kidney Dis* (2008). 51(4):651–62. doi:10.1053/j.ajkd.2007.12.023

308. Seminowicz, DA, Mikulis, DJ, and Davis, KD Cognitive Modulation of Pain-Related Brain Responses Depends on Behavioral Strategy. *Pain* (2004). 112(1):48–58. doi:10.1016/j.pain.2004.07.027

309. Habib, KE, Gold, PW, and Chrousos, GP Neuroendocrinology of Stress. *Endocrinol Metab Clin North America* (2001). 30(3):695–728. doi:10.1016/s0889-8529(05)70208-5

310. Kvetnansky, R, Sabban, EL, and Palkovits, M Catecholaminergic Systems in Stress: Structural and Molecular Genetic Approaches. *Physiol Rev* (2009). 89(2):535–606. doi:10.1152/physrev.00042.2006

311. Rivier, C, and Vale, W Modulation of Stress-Induced ACTH Release by Corticotropin-Releasing Factor, Catecholamines and Vasopressin. *Nature* (1983). 305(5932):325–7. doi:10.1038/305325a0

312. McEwen, BS, and Stellar, E Stress and the Individual. Mechanisms Leading to Disease. *Arch Intern Med* (1993). 153(18):2093–101. doi:10.1001/archinte.153.18.2093

313. Drossman, D Functional Abdominal Pain Syndrome. *Clin Gastroenterol Hepatol* (2004). 2(5):353–65. doi:10.1016/s1542-3565(04)00118-1

314. Hollande, F, Lee, DJ, Choquet, A, Roche, S, and Baldwin, GS Adherens Junctions and Tight Junctions Are Regulated via Different Pathways by Progastrin in Epithelial Cells. *J Cel Sci* (2003). 116(7):1187–97. doi:10.1242/jcs.00321

315. Lakatos, PL, and Burisch, J Environment and Invironment in IBDs: Partners in Crime. *Gut* (2015). 64(7):1009–10. doi:10.1136/gutjnl-2014-308460

316. Zhang, Y-Z, and Li, Y-Y Inflammatory Bowel Disease: Pathogenesis. *Wjg* (2014). 20(1):91. doi:10.3748/wjg.v20.i1.91

GLOSSARY

ACTH adrenocorticotropic hormone

ADHD attention deficit hyperactivity disorder

ATH adrenocorticotropic hormone

ANS autonomic nervous System

CD crohn's disease

CRF corticotropin releasing factor

CRP C-reactive protein

DASS depression, anxiety, stress scale

DMI depression in medically ill

DS-NA type D personality scale of negative affectivity

DS-SI type D personality scale of social inhibition

ENS enteric nervous system

F-calpro faecal calprotectin

GI gastrointestinal

HF high frequency

HRR heart rate reactivity

HRQOL health related quality of life

HRV heart rate variability

IBD inflammatory bowel disease

IL interleukin

IFN-γ interferon gamma

LF low frequency

LIMBO Study longitudinal course of inflammatory bowel disease study

MDP muramyl dipeptide

NOD2 nucleotide-binding oligomerization domain-like receptors 2

PAMPS pathogen associated-molecular patterns

PNS parasympathetic nervous system

PRR pattern recognition receptors

PSQ perceived stress questionnaire

PSQI pittsburgh sleep quality index

PVN para ventricular nucleus

QOL quality of life

RMSSD root mean square of the successive differences between N-N intervals

ROS reactive oxygen species

SDNN standard deviation of all normal R-R (N-N) intervals

SNS sympathetic nervous system

TGF-β transforming growth factor β

TLR toll like receptors

TNF-α tumour necrosis factor α

UC ulcerative colitis