# INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting functional disorder of the gastrointestinal (GI) tract with a range of symptoms that significantly affect quality of life for patients **(Lehrer, 2011).**

The presence of IBS is defined by clinical criteria, which include the presence of abdominal pain, or discomfort, and an alteration in bowel habit, in the absence of 'red flag' alarm features such as weight loss or anemia **(Manning et al., 1978).**

Pathophysiologies identified to date include gastrointestinal dysmotility, abnormalities in the inflammatory/ immune system, increase intestinal permeability, unstable or altered enteric flora, psychopathology, visceral and somatic hypersensitivity, and abnormal CNS processing **(Spiller et al., 2007).**

Misalignment that is a consequence of shift work is associated with an increased risk of developing cardiovascular, metabolic, gastrointestinal disorders, some types of cancer, and mental disorders **(Scheera et al., 2009).**

Change in circadian rhythm due to shift work has been associated with gastrointestinal symptoms such as abdominal pain, constipation and diarrhea. All of these symptoms resemble those observed in patients with functional bowel disorders (dyspepsia, irritable bowel syndrome etc.) **(Konturek et al., 2011)**.

# AIM OF THE WORK

The aim of this work is to determine whether disruption of sleep rhythms through the participation in shift work was associated with irritable bowel syndrome to better understand the association between disruptions in circadian rhythms and irritable bowel syndrome.

Chapter (1)

# IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a chronic relapsing and remitting functional disorder of the gastrointestinal (GI) tract with a range of symptoms that significantly affect quality of life for patients. In 1892, Osler coined the term *mucous colitis* when he wrote of a disorder of mucorrhea and abdominal colic with a high incidence in patients with coincident psychopathology. Since that time, the syndrome has been referred to by sundry terms, including spastic colon, irritable colon, and nervous colon **(Lehrer, 2011).**

The presence of IBS is defined by clinical criteria, which include the presence of abdominal pain, or discomfort, and an alteration in bowel habit, in the absence of 'red flag' alarm features such as weight loss or anemia. The first of these, the Manning criteria, were described over 30 years ago. Four symptoms were significantly more common among patients with IBS--namely, distension, relief of pain with bowel movement, looser and more frequent bowel movements with the onset of pain. Mucus and a sensation of incomplete evacuation were also common in these patients **(Manning et al., 1978).**

Subsequently, the Rome criteria were developed as a result of consensus of expert opinion **(Drossman et al., 1990).** These have been revised on two subsequent occasions to yield

Rome III criteria **(Drossman, 2006).** Manning criteria do not require a minimum duration of symptoms leading to a higher prevalence than the Rome criteria.

## Prevalence

IBS is a common condition, depending on how IBS criteria are defined, overall prevalence rates range from 5%-20% of the population in community surveys (**Hillilä and Färkkilä, 2004).**

In general Women are about 1.5-2 times more likely to develop IBS than men. Although it is present in all age groups, prevalence of IBS seems to decline with advanced age **(Rey and Talley, 2009)**.

The prevalence increases in those with coexisting functional GI diseases, particularly dyspepsia **(Ford et al. 2010).** IBS is also more common in patients with other functional disorders, such as fibromyalgia and chronic fatigue **(Riedl et al., 2008).**

# Pathophysiology

Irritable bowel syndrome is seen as a non-organic syndrome, primarily involving altered perception and processing of pain. As a result, the majority of current therapies for IBS revolve around stress reduction, alteration of pain pathways and alleviation of symptoms **(Ford et al., 2009).**

Others suggest the presence of evidence that IBS is an organic disease with a complex pathophysiology that is difficult to identify by standard diagnostic tools and it is variable from person to person and from children to adults **(Katiraei and Bultron, 2011).**

Pathophysiologies identified to date include gastrointestinal dysmotility, abnormalities in the inflammatory/ immune system, increased intestinal permeability, unstable or altered enteric flora, psychopathology, visceral and somatic hypersensitivity and abnormal CNS processing **(Spiller et al., 2007).**

- ***Gastrointestinal Dysmotility:***

Motor abnormalities of the gastrointestinal tract (GI) are detectable in some patients with IBS. Abnormalities observed include increased frequency and irregularity of luminal contractions, prolonged transit time in constipation-predominant IBS **(Agrawal et al., 2009)** and an exaggerated motor response to cholecystokinin and meal ingestion in diarrhea-predominant IBS **(Chey et al., 2001).** The relevance of these motor function alterations to symptoms has yet to be established. However, pharmacologic stimulation of gut motility in IBS patients has been reported to reduce gas retention and improve symptoms, suggesting that a motility disturbance underlies this complaint in some patients (**Caldarella et al., 2002**).

- ***Visceral Hypersensitivity:***

Visceral hypersensitivity (increased sensation in response to stimuli) is a frequent finding in IBS patients. Perception in the gastrointestinal tract results from stimulation of various receptors in the gut wall. These receptors transmit signals via afferent neural pathways to the dorsal horn of the spinal cord and ultimately to the brain. visceral hypersensitivity which is often triggered by bowel distention or bloating **(Posserud et al., 2007)** and which is often exacerbated by stress, is thought by many to be a determinant or biological measure of IBS **(Agrawal et al., 2008).**

It was found that altered rectal perception occur in large percentage of IBS patients in the form of either lowered sensory thresholds, increased sensation intensity or altered viscerosomatic referral, with a pain threshold of less than 40 mmHg in the rectum (elicited by balloon distension) correctly identified IBS from non-IBS subjects **(Bouin et al., 2002).**

It is unclear whether heightened sensitivity of the intestines to normal stimuli is mediated by the local GI nervous system by central modulation from the brain, or by some combination of the two **(Song et al., 2006).** In addition, other factors may contribute to visceral hyperalgesia, such as specific gastrointestinal mediators (serotonin, kinins) **(Faure et al., 2010)** or increases in spinal cord excitability due to activation

of an N-methyl-D-aspartate (NMDA) receptor **(Willert et al., 2004).**

The observations of gastrointestinal visceral hypersensitivity and increased viscero-somatic referral, along with reported increases in expression of extra-intestinal symptoms such as headache, dyspareunia, heartburn, muscle pain and back pain, and presence of fibromyalgia in some patients are consistent with a widespread aberrant central processing of pain (central sensitization) in these patients **(Whitehead et al., 2002 and Almansa et al., 2009).**

In addition, there are many studies suggesting that IBS patients may also be hypersensitive to somatic stimuli. One such study, showed hypersensitivity to rectal balloon distension and cutaneous thermal stimulation of the hand and foot in IBS patients. Interestingly foot hypersensitivity was greater than hand hypersensitivity, suggesting greater overlap of rectal and foot afferents at common lumbo-sacral levels (greater central hyperalgesia) than rectal and hand afferents at the levels of the cervical spinal **(Verne et al., 2001).**

It was found that peripheral mucosal insults, such as the presence of inflammation, injury or excess acid do not only increase pain sensitivity at the site of injury (primary hyperalgesia/peripheral sensitization) but also at more remote sites in the gastrointestinal tract (secondary hyperalgesia), via the process of central sensitization **(Knowles and Aziz, 2009).**

Another example of possible mechanisms of visceral hypersensitivity is the onset of IBS following GI infection (post-infectious IBS) where persistent sensitization of the primary afferents due to for example increased mast cells numbers, T lymphocytes, and expression interleukin (IL)-1β (peripheral sensitization), especially in the presence of risk factors such as depression, and adverse life events could lead to central sensitization and the persistence of symptoms, allodynia (pain to a stimulus that does not normally provoke pain), hyperalgesia (increase in intensity of pain to a stimulus that normally provokes pain), and dysmotility long after the resolution of illness **(Spiller and Garsed, 2009).**

- ***Stress and the Gastrointestinal-Neuro-Immune Axis:***

Stress in various forms predisposes individuals to developing IBS and increases IBS symptoms in children **(White et al., 2010).** Abuse or other significant stressors change the neurobiology of stress and alters the levels of corticotropin-releasing factor (CRF) (a peptide released from the paraventricular nucleus and a major mediator of the stress response). Corticotropin-releasing factor activates the pituitary-adrenal axis and mediates behavioral, autonomic, immune, and visceral responses to stress **(Gareau et al., 2008)**. Patients with IBS have enhanced stress responses and release higher amounts of CRF in response to stress **(Posserud et al., 2004).**

Stress changes the physiology of the gastrointestinal tract. Stressed human beings show similar findings to that found in animal studies in the form of CRF-mediated mucosal barrier dysfunction with macromolecular permeability and increased bacterial adherence/penetration of the gastrointestinal mucosa **(Gareau et al., 2006).** Also, there was mitochondrial swelling of the gut epithelial cells, immune cell infiltration, mucus depletion, and mast cell degranulation **(Gareau et al., 2008)**.

Stress induces inflammation through numerous pathways. Corticotropin-releasing factor can directly influence human colonic mast cells **(Wallon et al., 2008)**, which then induce intestinal epithelial pathophysiology and mucosal barrier defects **(Saunders et al., 2002)**.

Substance P (SP) and calcitonin gene-related peptide (CGRP)-containing gastrointestinal efferent neurons can also influence mast cells and result in degranulation and release of TNF-α **(De Jonge et al., 2004)** and **(Santos et al., 2005).** These compounds, in turn, result in gut inflammation and increase intestinal permeability **(Stead et al., 2006).**

These stress-induced changes in the gastrointestinal tract persist after the stressor is removed. This is likely to be due to the ability of mast cells to influence their environment. In rats, inflammation results in increased mast cell-neuronal contacts and mucosal nerve cell density that last well beyond the initial

insult **(Stead et al., 2006).** Gastrointestinal inflammation in humans also results in neuron proliferation **(Wang et al., 2004).** Stress and inflammation modulate nerve growth factor (NGF), which then affects mucosal nerve remodeling, sprouting, and synaptogenesis. Mast cells, in close contact with neurons, synthesize and release NGF, and thus, can alter neuronal density and synaptogenesis **(Barreau et al., 2008).**

Furthermore, inflammation preceding a psychological stress can alter the epithelial response to stress signals and make the gut more susceptible to stress. In addition, inflammation can change the morphology of mast cells and their intracellular contents, further changing the susceptibility of the gut to various future stressors (**Saunders et al., 2006**)

Inflammation can play an important part in the manifestation of IBS symptoms. Once the inflammatory cascade is activated, this immune response can create a vicious cycle of self-perpetuating inflammation. Activated mast cells can directly release CRF **(Theoharides et al., 2004).** Patients with inflammatory bowel disease (IBD) and IBS have CRF, immunoreactive macrophages, enterochromaffin cells, lymphocytes, neutrophils, and eosinophils, which are present in higher concentrations than in healthy controls (**Cremon et al., 2009**). Corticotropin-releasing factor induces lymphocyte proliferation and macrophage release of pro-inflammatory cytokines (TNF-α, IL-1, and IL-6). These activated immune cells, in turn, locally release CRF and other immune peptides,

which then activate mast cells. Mast cell-derived tryptase is a compound that recruits lymphocytes, eosinophils, and macrophages, and can further perpetuate inflammation **(Kiank et al., 2010)**.Tryptase in IBS patients can stimulate calcium signals in dorsal root ganglion neurons, leading to activation of these neurons. The proximity of mast cells to nerve terminals in the intestine has also been correlated with the severity of abdominal pain **(Barbara, 2006).**

- ***Serotonin and Irritable Bowel Syndrome:***

Serotonin (5-HT) can influence the motor function and sensitivity of the gastrointestinal tract **(Spiller, 2007)**. Serotonin exerts a range of effects via its seven receptor subtypes (5-$HT_1$ to 5HT-$_7$). Serotonin receptor $5HT_5$, $5HT_6$, $5HT_7$ are found in the brain, whereas $5HT_1$, $5HT_2$, $5HT_3$, $5HT_4$, and $5HT_7$ are the gastrointestinal serotonin receptors **(Sikander et al., 2009).**

A large majority of the body's serotonin is stored in gastrointestinal enterochromaffin cells (EC). Patients with diarrhea predominant IBS have increased EC cells (**Dunlop et al., 2003**), which are activated by inflammation to release serotonin and may result in the elevated serotonin levels found in patients with IBS **(Wang et al., 2007).**

Serotonin reuptake transporters (SERT) in the gut epithelial cells terminate the effects of serotonin and influence serotonin concentrations and symptoms of IBS. Patients with IBS have genetic polymorphisms that lead to lower expression of transport proteins and less serotonin reuptake **(Kohen et al., 2009).** The noted inflammation may also alter SERT expression and decrease its function in patients with IBS (**Mawe et al., 2006**).

- ***Intestinal Permeability, Chronic Inflammation and Antigens:***

The presence and activity of mast cells, along with other inflammatory cells, alone are not likely result in chronic inflammation. Other intestinal antigens, such as food, bacteria, and fungi are likely to be needed to perpetuate the inflammation in the presence of an impaired gastrointestinal epithelial barrier **(Cenac et al., 2004).**

Healthy individuals have tight junctions that help to form the gastrointestinal epithelial barrier along with mucous, secretory IgA and other peptides. This epithelial barrier controls the interaction between luminal bacteria and antigens and the mucosal immune system **(Kraehenbuhl and Corbett, 2004).** It also allows immune tolerance of food antigens and bacteria. Activation of colonic proteinase-activated receptor (PAR2) not only leads to neuronal activation, but also to

epithelial barrier defects in patients with IBS **(Cenac et al., 2004).**

Low level PAR2 activation of the myosin light chain kinase (MLCK) causes phosphorylation of the myosin light chain, which then leads to contraction of the actin-myosin ring. Tight junction protein zona occludens-1 (ZO-1) re localizes into the cytoplasm and disrupts the tight junctions, which increases paracellular permeability. High level PAR2 activation in the rat colon results in localized inflammation and increased production of TNF-α and IFN-γ. IFN-γ decreases ZO-1 expression and alters the actin cytoskeleton organization. TNF-α activates MLCK and results in tight junction protein relocation **(Ye et al., 2006 and Ma et al., 2005).**

Children and adults with IBS have increased intestinal permeability. Increased intestinal permeability results in mucosal barrier defects that allow the passage of an increased load of luminal antigens of dietary and bacterial origin which, in turn, elicit the activation of mucosal immune responses **(Barbara, 2006).**

Various triggers can activate mast cells. Bacteria are powerful antigens for the gastrointestinal immune system **(Rautava and Walker, 2007).** Stress can result in increased bacterial adherence and penetration into the gastrointestinal mucosa (**Gareau et al., 2008**), which may increase the

interaction between the luminal bacteria and local immune response.

This may explain why patients with IBS have higher antibody titers to specific bacterial flagella than healthy controls. The DNA of these bacteria can interact with toll-like receptors, which then influence the immune system through regulation of tumor necrosis factor alpha and interferon gamma (**Schoepfer et al., 2008**).

Escherichia coli, Campylobacter, and other bacteria can negatively influence the GI immune system and result in gastrointestinal inflammation and intestinal permeability (**Wang et al., 2004**). Conversely, commercially available beneficial bacteria, in the form of probiotics, can reduce gastrointestinal inflammation **(Peran et al., 2007)**, reverse or prevent intestinal permeability, and stop bacterial adhesion and translocation **(Zareie et al., 2006).**

Probiotics can also reverse visceral hypersensitivity from various causes, including stress **(Eutamene et al., 2007).** Probiotics attenuate the upregulation of pain pathways at the spinal and supraspinal levels **(Ait-Belgnaoui et al., 2009)**, and induce epithelial cells to express micro-opiate receptor 1 (MOR1) and cannabinoid 2 (CB2) opioid receptors. Thus, probiotics can reduce the symptoms of IBS **(Hoveyda et al., 2009).**

Adults with IBS have gastrointestinal microflora that are significantly different than those of healthy populations

**(Kassinen et al., 2007).** Children with IBS are also likely to have significant alterations in their gastrointestinal microflora. It was speculated that there may be a subset of children who are predisposed to developing IBS through repeated or prolonged exposure to antibiotics for various reasons (recurrent otitis media, sepsis, meningitis, osteomyelitis, vesicoureteral reflux, acne, *etc*). Various antibiotics, including Augmentin, the macrolides, and amoxicillin significantly alter the composition of the bacteria in the GI tract. Antibiotic use has been related to increased rates of IBS and functional abdominal pain **(Maxwell et al., 2002).**

Gastrointestinal bacteria are also influenced by the diet. Dietary soluble fiber encourages the growth of beneficial species like lactobacilli and bifidobacteria. In mice, a white bread diet significantly prolonged antibiotic induced bacterial perturbations. It is common knowledge that diet which lacks fiber, may predispose human beings to have prolonged antibiotic induced bacterial perturbations **(Delzenne, 2003).**

Prebiotics are short chain carbohydrates that help some of the beneficial bacteria or probiotics in the intestines to grow more effectively. Prebiotics may decrease IBS symptoms **(Silk et al., 2009).** Prebiotics are fermented by probiotics and metabolized into short chain fatty acids (SCFA). SCFAs can decrease inflammation and are used in maintaining the intestinal epithelial lining **(Macfarlane et al., 2006).**