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## **CHAPTER 1 INTRODUCTION**

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## BACKGROUND

### 1.1.1 OVERVIEW AND RESEARCH OUTLINE

Functional gastrointestinal disorders (FGID) are the most common and yet incompletely understood problems in gastroenterology practice and in the community. The largest subgroups of affected patients, usually women, suffer from irritable bowel syndrome (IBS) and functional (non-ulcer) dyspepsia (FD), each reliably defined as a distinct and homogeneous entity by a constellation of symptoms supported by the absence of mucosal disease or biochemical abnormalities (Drossman et al, 1990a). There is considerable *overlap among these syndromes* with many patients fitting more than one category (Drossman et al, 1990a).

*The course of IBS/FD is generally chronic, fluctuating and recurrent* with very few patients (9%) becoming symptom-free within two years (Bleijenberg & Fennis, 1989). In the context of a poorly understood etiology and pathophysiology, specific diagnostic tests and specific treatments are unavailable and management can be difficult. The social and economic implications are considerable, therefore, in terms of individual suffering, increased medical workload and significant financial cost. IBS and FD, of themselves, are a source of substantial morbidity and cost to the community.

*A core feature of the phenomenology of FGID is psychological distress.* Studies consistently report high levels of anxiety and depression in patient and community subjects with IBS (Jarrett et al, 1998). Psychiatric studies report that, on average, half of patients with IBS or FD have a concurrent psychiatric disorder - almost always, anxiety and depressive disorders (Talley et al 1993; Mishra, et al, 1984). A variety of other stress-related symptoms such as fatigue, headaches

and insomnia, loosely termed 'somatization', also coexist frequently with FGID (Whorwell et al, 1986a; Colgan et al, 1988).

*Issues of causality concerning coexistent psychological morbidity have not been adequately addressed.* It is possible that anxiety, depression and other psychological symptoms may be secondary to symptoms that are persistent, often unpredictable, and for which no 'organic' explanation can be found. Alternatively, as the psyche affects both functional gastrointestinal (GI) processes and their subjective perception (Kellow et al, 1991; Wolf, 1981), it is plausible that stress reactions may be involved in the development and exacerbation of functional GI (and non-GI) symptoms, particularly when the distressed state is intense and prolonged or is combined with a low constitutional threshold for stress (Lagarde & Spiro, 1984; Camilleri et al, 1986a).

Consistent with this, *personality traits* and illness-related attitudes that predispose to a more intense and prolonged stress response also have been implicated in the development of IBS/FD (Talley et al, 1998; Langeluddecke et al, 1990). Levels of neuroticism and trait anxiety are higher in individuals with IBS/FD compared with healthy subjects (Talley et al, 1986) and other patient groups (Palmer et al, 1974). These personality traits can be expected to increase vulnerability to stress (Nurcombe & Gallagher, 1989). They may also predispose individuals to adopt ineffectual stress management (or coping) skills. No personality has been found that is unique to IBS or FD and although Chaudhary and Truelove (1962) observed that excessive worriers have a poor outcome long-term, this had not been demonstrated formally.

*Life stress* also has been strongly implicated in the etiopathogenesis of IBS. Most people with IBS/FD recall a distressing episode that preceded the onset of their symptoms (Chaudhary & Truelove, 1962), most believe their symptoms to

be exacerbated by stress (Waller & Misciewicz, 1969) and early observations suggest that symptoms either disappear or improve following resolution of major life stress problems (Chaudhary & Truelove, 1962). Also, an impressive and sustained improvement in symptoms occurs following the acquisition of more effective stress-management skills (Guthrie et al, 1991; Shaw et al, 1991; Rumsay, 1991). Despite the general belief of patients, their clinicians and the general public that life stress influences the onset and course of the disorder, empirical evidence from formal studies is inconclusive.

A strong and consistent association between exposure to life stress and the subsequent onset or exacerbation of IBS/FD, especially when stressors are chronic and highly threatening (Bennett et al, 1991), has been reported by a small number of studies using comprehensive interview-based methods (Craig & Brown, 1984; Creed et al, 1988; Bennett et al, 1991). In contrast, formal studies of life events and daily hassles using questionnaire methods are highly inconsistent in their findings and even when life stress effects are significant, they are small (Whitehead et al, 1992). The extent to which life stress contributes to the course of IBS/FD symptoms therefore remains uncertain (Whitehead, 1994; Drossman, 1996a).

Consequently, the purpose of this work was to investigate issues not previously addressed. *A research outline is presented in Table 1.* The first two studies address issues relevant to the relation of psychosocial factors - in particular chronic life stress, psychological distress and personality - to the number and type of FGID and to the course of symptom intensity in IBS over time. The last three studies address issues concerned with relations between psychosocial factors and GI transit, motor and sensory function in FGID, alterations in the latter parameters being the putative origin of symptoms in the FGID.

Of particular relevance to all studies is the use of: 1) *a recently compiled symptom classification system for FGID* (the “Rome” criteria); 2) *a superior objective method of life stress assessment (The Life Events and Difficulties Schedule (LEDS))*; and, 3) *sophisticated and sensitive technologies* which have been responsible in recent years for quite remarkable progress in understanding and identifying human function and dysfunction throughout the GI tract. Novel features include measures based on both the nature and the course of IBS and FD.

Addressing these issues has implications not only for an improved understanding of the psychophysiological mechanisms involved in the development and exacerbation of symptoms and/or sensorimotor disturbances in FGID, but importantly, for improved patient care.

#### 1.1.2 DEFINITIONS

More than half of the patients referred by their general practitioner for gastroenterological assessment complain of chronic abdominal symptoms, but conventional diagnostic tests show no structural or biochemical disease. Their underlying pathophysiology is unknown. In the absence of an identifiable organic cause these clinical conditions are labelled as ‘functional’ GI disorders. A diagnosis of one or more FGID (Appendix A) is determined only after endoscopic, radiologic, or histologic evidence has excluded ‘organic’ disease and the presenting symptoms satisfy appropriate diagnostic criteria.

The currently accepted diagnostic criteria for FGID (Drossman et al, 1994) was reached by consensus at an international working party of experts in Rome in 1989 and again in 1992. The FGID assessed in this study are tabled in Appendix B. The major groups include the functional gastroduodenal disorders and the functional bowel disorders. The disorder of special interest in this work are FD

**Table 1** Research outline

<b>IN PATIENTS WITH FUNCTIONAL GASTROINTESTINAL DISORDERS (FGID) -                      THE RELATIONSHIP OF PSYCHOSOCIAL FACTORS (STRESS, DISTRESS AND PERSONALITY) TO:</b>			
SYMPTOM-RELATED OUTCOMES	GASTROINTESTINAL MOTILITY OUTCOMES		
	TRANSIT	MOTOR (CONTRACTILE) ACTIVITY	SENSITIVITY (PERCEPTION)
<u>Assessment Features:</u>			
‘ROME’ DIAGNOSTIC CRITERIA	SCINTIGRAPHY	MANOMETRY / DISTENSION	
<u>Study 1.</u> <b>Cross-sectional symptom outcomes:</b> <ul style="list-style-type: none"> <li>• number of FGID</li> <li>• type of FGID</li> <li>• extraintestinal (somatic) symptoms</li> </ul> <b>‘Process’ suggested by these data</b>	<u>Study 3.</u> <b>Delay in Transit in one region (the stomach):</b> <ul style="list-style-type: none"> <li>• 4 parameters of solid emptying</li> <li>• 2 parameters of liquid emptying</li> </ul>	<u>Study 5.</u> <b>Small bowel motor abnormalities</b> <ul style="list-style-type: none"> <li>• postprandial motor activity</li> <li>• fasting motor activity</li> </ul>	
<u>Study 2.</u> <b>Life Stress and symptom intensity over 16mo:</b> <ul style="list-style-type: none"> <li>• patterns of change over three time-periods</li> <li>• covariance</li> <li>• time-lag predictions</li> <li>• clinical outcome</li> <li>• role of depression</li> </ul>	<u>Study 4.</u> <b>Delay in transit - in three regions (the stomach, small bowel and colon)</b> <ul style="list-style-type: none"> <li>• delayed transit (DT) per se</li> <li>• widespread delay in transit ie delay in two or more regions</li> <li>• normal transit in all three regions</li> </ul>	<b>Small bowel sensory abnormalities</b> <ul style="list-style-type: none"> <li>• initial perception</li> <li>• pain threshold</li> </ul>	<b>Subgroup comparisons</b> <ul style="list-style-type: none"> <li>• sensorimotor</li> <li>• motor</li> <li>• fasting motor abnormalities</li> </ul>

and IBS - one (or both) of these subgroups is included in each study. As with all FGID, IBS and FD are symptom-based diagnoses.

### **Irritable bowel syndrome (IBS)**

In the absence of other recognisable disorders, *IBS is defined by the presence of chronic or recurrent abdominal pain of at least three months duration together with an associated alteration of bowel function (constipation, diarrhea or alternating constipation and diarrhea) with bloating or abdominal distension that increases through the day.* Other symptoms may include altered stool frequency, altered stool form, or passage, or the presence of mucus. Fatigue and lethargy are also common, but not diagnostic. Several studies using different methodologies suggest that the Manning criteria (Manning et al, 1978), the precursor of the present “Rome” criteria for IBS, may be less specific for males (Greenbaum et al, 1987; Talley et al, 1990b; Smith et al, 1991).

### **Functional dyspepsia (FD)**

*Dyspepsia is defined currently as persistent or recurrent abdominal pain or abdominal discomfort centered in the upper abdomen* (Talley et al, 1994). The majority of dyspeptic patients have FD - that is, after clinical investigation has excluded approximately one third who on routine physical examination and laboratory investigation are found to have peptic ulceration, reflux oesophagitis and/or upper gastrointestinal malignancy (Talley & Piper, 1985). Each subgroup of FD is distinguished from others by a specific cluster of symptoms detailed in Appendix B. The predominant complaint of patients with *ulcer-like dyspepsia* is chronic upper abdominal pain which may be well localised to the epigastrium or it may be periodic with remissions and relapses. The pain may waken the person

from sleep and may be relieved by food, antacids or histamine (H<sub>2</sub>) blockers. The symptoms are highly suggestive of peptic ulcer disease. The prominent complaint of patients with *dysmotility-like dyspepsia* is chronic upper abdominal discomfort which includes symptoms such as early satiety, postprandial discomfort, fullness or bloating. These symptoms suggest an underlying motility disturbance of the upper gut (Kellow, 1992). Although not currently included as a Rome FD subgroup, *reflux-like dyspepsia* as defined in earlier versions as dyspepsia plus heartburn and/or regurgitation at least once a week for three months or more (Drossman et al, 1990a) has been included because these latter symptoms frequently overlap with ulcer-like dyspepsia, dysmotility-like dyspepsia and with IBS. *Unspecified dyspepsia* comprises symptoms of FD that do not fit any of the other categories.

As well as reflecting a lack of understanding of the underlying pathophysiology of this group of disorders, terms such as x-ray negative dyspepsia, pseudo-ulcer syndrome, nervous dyspepsia, non-organic dyspepsia, non-ulcerdyspepsia and now functional dyspepsia, continue to illustrate the extent to which psychological disturbances is regarded as an important feature of these disorders.

### 1.1.3 EPIDEMIOLOGY

FGID are common conditions with socio-economic implications that are considerable in terms of individual suffering, inappropriate management, days lost from work, increased medical workload and significant financial cost (e.g. Drossman et al, 1993).

## **Irritable bowel syndrome**

More than one in seven people in the Australian community suffer from IBS, representing approximately 10% of the total attendance to general practitioners (Talley et al, 1997) and up to half of the consultations with gastroenterologists (Sandler et al, 1984; Talley et al, 1995). Estimates from some regions of the United States are somewhat higher, suggesting that symptoms compatible with a diagnosis of IBS may affect up to 22% of the general population (Drossman et al, 1993). Generally IBS is reported as being more prevalent in women (especially younger women) (15-25%) than in men (5-20%) (Drossman et al, 1993).

IBS follows a chronic, fluctuating and recurrent course displaying changes in symptom severity and diagnostic category over time. Interestingly, the overall prevalence in the general community remains relatively stable as individuals move in and out of the category of IBS as their symptoms fluctuate (Waller & Misiewicz, 1969; Locke et al, 1996; Agreus et al, 1995). Although a substantial proportion fail to satisfy criteria for IBS in a 12 month period (Talley et al, 1992a), only as few as 9% experience a complete recovery within 2 years (Bleijenberg & Fennis, 1989). Symptoms begin before the age 35 in 50% of patients and 40% of IBS patients are aged 35 to 50 years. IBS is recognised in children, and many patients can trace the onset of their symptoms back to childhood. People with IBS are more likely also to have a history of surgical procedures such as hysterectomy and appendectomy. Onset in old age is rare, and may suggest organic pathology.

While prevalence rates are remarkably stable across countries, the proportion who consult for IBS symptoms varies considerably. Using rigorous diagnostic criteria Talley and co-workers (1997) found that 73% of an Australian community population had seen a gastroenterologist for their IBS symptoms in

the previous year. This is similar to reports from the United Kingdom (Heaton et al, 1992) of consultation rates of 75% for men and 76% for women with five or more IBS symptoms, but contrasts with studies in the US which found as few as 25% of Americans consulted for IBS symptoms (e.g. Talley et al, 1991a). Among those who consult for their IBS symptoms women predominate in western cultures (Thompson et al, 1994).

### **Functional dyspepsia**

FD is also very common, on average affecting up to 30% or more of individuals (Jones & Lydeard, 1989; Hu & Talley, 1998). Jones and Lydeard (1989) report that only 35% have never experienced dyspepsia. Although a minority of sufferers (25%) seek medical help in a given 6 month period (Jones & Lydeard, 1989), in general practice FD ranks fourth in frequency among all diagnoses (Adami et al, 1984) and is at least three times as common as peptic ulcer disease (Thompson & Heaton, 1980). There are no consistent gender differences in prevalence, but the proportion with FD increases with age, probably due to an increased prevalence of heartburn in the elderly (Jones & Lydeard, 1989).

The social and economic implications of FD are considerable in terms of absenteeism from work, interference with daily activities and the cost of diagnostic procedures. Extrapolating to Australian conditions from the Scandinavian data of Nyren and colleagues (1985b), Bolin and Korman (1992) calculate that if the cost of outpatient care, drugs, lost earnings and sick leave benefits are taken into account the annual cost would exceed 400 million Australian dollars.

## **Overlap among functional gastrointestinal disorders**

It is well recognised that although symptom-based FGID groups and subgroups can be identified, they are interrelated in their pathophysiology and clinical expression and frequently coexist (Drossman et al, 1994). For patients with FD, for example, IBS and/or gastro-oesophageal reflux are present in almost 70% of cases (Talley & Piper, 1985). Only one quarter present with no associated FGID, and these have been termed ‘essential (or idiopathic) dyspepsia’. This term is used in the literature review to distinguish this more restrictive subgrouping from those with functional (non-ulcer) dyspepsia which prior to the current classification system included FD patients with and without IBS.

### **1.1.4 ALTERED DIGESTIVE TRACT FUNCTION IN IBS/FD**

The belief that the psyche plays an important role in the functioning of the bowel is legendary, and the interrelatedness of the psyche and bowel is apparent in both health and in gastrointestinal (GI) disorders. New technologies have improved our understanding of disorders of gut motility, disorders of gut sensitivity, and their relation to central nervous system functions. These interrelationships are of course relevant to many digestive tract disorders, but a particular focus of interest has been the IBS, the most common of the functional group of GI disorders, and FD. ‘Stress’ including emotional distress and life event stress is strongly implicated in these disorders. The following sections will report epidemiological evidence of higher levels of emotional distress among IBS/FD patients, and more frequent exposure to stressful life events prior to onset of symptoms, than among healthy individuals. Through the availability of increasingly more sophisticated technologies it has become evident, for

example, that multiple brain-gut factors are involved in the phenomenology of FD and IBS. Each of the following appear to contribute to IBS/FD symptom development through complex interactive processes:

### **Dysmotility and altered transit**

*In health*, as a meal begins, the motility and secretion pattern of the digestive system alters. The proximal stomach becomes tonically relaxed and phasic contractions are peristaltic to facilitate the transport of food from the stomach to the duodenum for absorption. When the stomach is almost empty, this 'fed' pattern is followed by a fasting phase. *The small intestine undergoes bursts of cyclical motility (migrating motor complexes (MMC))*. These bursts slowly traverse the bowel, removing residual food and cellular debris to prevent stasis and bacterial overgrowth. After eating, this pattern is abolished and replaced by contractions which both mix and slowly propel chyme distally. In contrast to the small bowel, the movements of the large intestine are less well understood; cyclical activity is not likely to occur, contractions in general are less frequent, and yet from time to time powerful migrating contractions sweep through the entire colon.

*In FD and IBS*, gastric emptying, especially of solid food, may be delayed. Manometric examination may find that the antrum contracts with insufficient frequency and strength (postprandial antral hypomotility) to adequately grind the solid constituents of the meal, while in some FD patients, the proximal part of the small intestine may also be involved and MMC activity is disturbed (intestinal motor dysfunction). These abnormalities are found in approximately half of patients with FD (You et al, 1980; Waldron et al, 1991). In patients with IBS, motor dysfunction has been documented in most regions of the GI tract, most

commonly in the small and large intestine. Some of these disturbances are meal related, some are not. Prolonged recordings of small bowel motility reveal that, during the fasting phase, MMCs can occur with greater frequency in patients with IBS and diarrhoea than in those with predominant constipation or healthy controls. Abdominal pain can occur concurrently with episodes of clustered contractions in the jejunum, or with powerful peristaltic contractions in the ileocolonic segment, the latter providing one of the few strong links between disturbed motor patterns and symptoms (Kellow et al, 1988). In IBS patients whose predominant bowel habit is constipation, colonic transit can be slowed by too many contractions (spasms) or by too few (atony), whereas hypomotility of the sigmoid colon appears to be associated with predominant diarrhoea. In some patients with IBS, the postprandial 'gastrocolic' response occurs late, but persists longer; this may be related to the discomfort experienced by some patients after meals. It is interesting that in recurrent IBS, these GI motor disturbances may only be present during the symptomatic (and not the asymptomatic) stage.

Alterations in the normal patterns of stomach and bowel motility are thought to cause many of the symptoms of FD/IBS. Factors influencing such changes may include eating (eg caloric load / fat content), life stress or menstrual cycle. Uncoordinated or abnormally high pressure contractions may cause excessive distension or stretching of the bowel wall directly, or may produce other effects such as trapping of packets of gas which then distend the bowel. Each of these effects may give rise to abdominal pain or discomfort. Impairment of propulsive activity, or conversely an excessive number of contractions, may lead to abnormal movement of food residue through the gut. *Delayed transit* of food results in a range of symptoms from nausea and vomiting to abdominal pain and/or constipation, depending on the region

affected. Delayed emptying from the stomach can cause loss of appetite, nausea, inability to eat a normal sized meal, vomiting, belching and bloating. Delayed transit through the colon can produce constipation or abnormally hard stools. *Accelerated transit* through the small and large bowel may result in abdominal pain, also diarrhoea.

In most patients with IBS/FD, however, symptoms cannot be explained on the basis of motor dysfunction alone. Indeed, in some patients with FD, gastric motility, secretion and emptying all appear to be normal (Camilleri et al, 1986b; Scott et al, 1993a; Tucci et al, 1992). Also, symptoms do not always coincide with abnormal contraction patterns (Kellow & Phillips, 1987; Kumar & Wingate, 1985; Achem et al, 1992) even though psychological stress produces both symptoms (Almy et al, 1949a; Drossman et al, 1982) and dysmotility in healthy controls and patients with FGID (Kellow & Phillips, 1987; Welgan et al, 1988). Sometimes however, the clinical manifestation of a disorder is best understood in terms of sensorimotor (motility and sensory) abnormalities. For example, rectal sensitivity together with colonic and/or small bowel motor abnormalities provides the best explanation for small or normal stools (but passed frequently), small, hard, pellet-like stools that are more difficult to expel than larger stools, and a feeling of incomplete emptying. The relation of sensory and motor disturbances to symptoms in FGID is currently an area of considerable interest and debate (Weiner, 1992; Mayer & Gebhart, 1994; Mayer, 1996b; Drossman, 1996b). The relation of psychosocial factors to sensory and/or motor dysfunction is also poorly understood.

## **Hypersensitivity**

Hypersensitivity (hyperalgesia) of the gut, now a well-recognised phenomenon in all regions of the GI tract, appears to explain why a greater proportion of patients frequently perceive normal (but powerful) contractions as abnormal sensation. Some may even experience pain with normal, as well as abnormal, contractile activity. Indeed, a generalised hypersensitivity of the gut has been hypothesised for some IBS patients; balloon distension studies of the oesophagus, stomach, and small and large bowel can both induce and reproduce pain anywhere in the abdomen. Patients with FD report bloating, discomfort or pain at lower volumes of intragastric balloon distention than in non-dyspeptic volunteers (Mearin et al, 1991; Coffin et al, 1994) while gastric dysrhythmias may help to explain early fullness for some (Koch, 1993). In addition to enhancing the perception of gut contractions, hypersensitivity also affects motor function. As mentioned above, when the rectum is hypersensitive even small amounts of stool can elicit the defecation urge.

In patients with FD, the presence of gastric hypersensitivity appears to be independent of helicobacter pylori infection and duodenitis (Azpiroz, 1996; Hu & Talley, 1998). It also seems to be restricted to the gut in FD, that is, in patients with gastric hypersensitivity, somatic (non-gut) sensitivity (as assessed by both cold pressure test and transcutaneous electrical nerve stimulation) is normal (Coffin et al, 1994; Mearin et al, 1991). Intestinal infections, such as acute bacterial gastroenteritis, appear to be one of the local factors which can sensitise the nervous system in the bowel to overreact to normal stimuli. "Post-infective" irritable bowel account for up to 25% of cases of IBS, emphasising the importance of recognising different subgroups of the disorder. Sensitivity in the small intestine has been found in patients with IBS (with or without FD) but

not in FD alone (Accarino et al, 1995). Altered perception in IBS/FD has been linked to dysfunction of gut reflexes, but many of these more subtle forms of GI dysfunction still remain to be characterised (Azpiroz, 1996). The relation of hypersensitivity to dysmotility also needs further study.

### **Central Nervous System - Enteric Nervous System Dysregulation**

The movements of the stomach and intestines are primarily under the control of the autonomic nervous system. The gut wall also has its own nervous system, the enteric nervous system (ENS) or the 'little brain of the gut' which is well connected to the central autonomic neural network in the central nervous system (CNS) through both motor and sensory pathways of the sympathetic and the parasympathetic nervous systems. While the ENS can operate independently to co-ordinate and integrate the activities of the stomach and intestines, the CNS has the important role of co-ordinating the diverse functions of the ENS. This means that apart from swallowing and defecation (or retention), all other activities of the gut proceed automatically. It also means in effect that the 'hardwiring' between the CNS and gastrointestinal activity ensures a reciprocal relation between the events of the psyche and that of the bowel.

Interrelations between dysfunctions in the brain and in the gut has been an area of active research during the past decade. For example, in IBS patients, cerebral responses to visceral pain are altered compared with healthy controls (Silverman et al, 1997) as is altered cerebral function during REM sleep (Kumar et al, 1992). These studies suggest that dysregulation of the brain-gut axis occurs in IBS. It has been suggested (see below) that neuroplastic changes within the CNS (i.e. use dependent changes in neuronal plasma membrane receptors, ion channel expression and changes in synaptic efficiency in response to the internal

or external environment), which may be activated by subsequent internal or external stressors, may play an important role in the expression of functional GI disorders such as IBS (Mayer & Gebhart, 1993).

### **Stress and gut function**

Activation of the generalised stress response by environmental events perceived as stressful heightens arousal, improves attention and cognitive function, decreases appetite and sexual arousal, increases the tolerance of pain and has profound effects on GI function (Mayer, 1996b). Considerable experimental evidence suggests that the principal mechanisms of the generalised stress response involve a positive feedback loop between the hypothalamic neurons secreting the peptide corticotrophin-releasing hormone (CRH) and the locus coeruleus-norepinephrine systems in the brainstem. Both behavioural and colonic alterations involve the stimulation of hypothalamic CRH-secreting neurons and the associated activation of neuroendocrine (hypothalamic-pituitary-adrenal [HPA] axis) and autonomic systems. Neuroplastic changes, a characteristic response of the nervous system to intense or prolonged perturbations of the internal or external environment, recently have been documented using positron emission tomography in patients with IBS (Silverman et al, 1995). These structural changes on a cellular receptor level have profound influences on the ability of the organism to shut off the stress response appropriately once the stressful event is over (Mayer & Gebhart, 1993).

### **Key Issues:**

1. The variable symptomatology and pathophysiology of IBS and FD suggests that these disorders may be triggered by a number of different factors.

2. Dysmotility and hypersensitivity of the intestine are prevalent in both IBS and FD.
3. In the hypersensitive gut, normal (as well as abnormal) motility patterns may be perceived as abnormal sensation.
4. A generalized hypersensitivity of the gut has been hypothesised for some IBS patients.
5. Sensorimotor dysfunction has been found in most sites in the GI tract of patients with IBS; most commonly it is the small and large intestine that is affected.

Given that the ‘hardwiring’ underlying the interrelatedness of brain and gut functions is now well established and the relation of life stress to functional GI symptoms can be presumed (Drossman, 1992), it remains for research to empirically show that life stress does or does not influence the onset or exacerbation of these disorders. The following sections review in detail, the relation of psychological and social (life stress) factors to IBS/FD and to altered gut function in these disorders. The primary focus is their relation to the onset or exacerbation of these disorders. Given the interrelatedness of brain-gut mechanisms an attempt is made to address issues of cause and effect wherever possible.

## **1.2 PSYCHOLOGICAL ASPECTS OF IBS/FD**

The pathogenesis of IBS and FD in general, and the role of psychosocial factors in particular, are issues attracting increased scientific attention as evidenced by at least a twofold increase in the number of research papers and reviews published on the subject since 1990. The literature is summarised in

Appendices C to F. Summaries of formal studies of the *psychological status* of patients with IBS and FD from 1960 to 1998 are presented in Appendices C for cross-sectional studies, and D for longitudinal studies. Similar summaries assessing *life stress* in IBS and FD are presented in Appendices E and F for cross-sectional and longitudinal studies respectively. The first part of this review (sections 2 and 3) critically evaluate the relation of psychological and life stressors factors to IBS and FD; the second (section 4), addresses the relation of psychosocial factors to altered function in IBS/FD. The literature in this section will be considered under three major headings: 1) *psychological morbidity in IBS/FD*; 2) *personality, coping and IBS/FD*; and 3) *life stress in the etiology of IBS/FD*.

## 2.1 PSYCHOLOGICAL MORBIDITY IN IBS/FD

### **A brief historical perspective**

In the absence of a structural/organic explanation, IBS was initially considered primarily as a psychopathological condition and research findings of the day were interpreted as supporting this view. With some notable exceptions, for example, Chaudhary and Truelove's seminal observations in 1962, the presence of unexplained abdominal pain together with the disturbed and/or erratic bowel symptoms of IBS was explained almost entirely in terms of intrapsychic functioning. Unexplained pain was attributed to a pain-prone personality; the pain representing a means of emotional expression (Engel, 1974). Patients with these symptoms were considered to be hypochondriacal, (Hill & Blendis, 1967) or their condition psychogenic (Hislop, 1971). Even a diagnosis of 'functional' (ie in contrast to organic) was based on reports of 'non-

organic' abdominal pain and bowel dysfunction (Gomez & Dally, 1977) rather than a positive diagnosis based on the presence of psychiatric illness or bowel disorder. IBS was considered therefore to be part of a diagnosable psychiatric illness (Liss et al, 1973) or more specifically, a manifestation of an underlying affective disorder (Latimer et al, 1979a) rather than a distinct entity. This view of IBS as a manifestation of 'illness behaviour', whereby normal function is perceived as abnormal, persisted through several decades with remnants still apparent today (Nyhlin et al, 1993) even though at least some patients with IBS have never had a psychiatric disorder (Creed & Guthrie, 1987). In other patients with IBS psychological disturbance is non-specific in terms of a psychiatric diagnosis (eg Latimer et al, 1981), being described as psychological distress by many (eg. Magni et al, 1985). A positive outcome of the research generated during this period, despite the somewhat pejorative implications underlying the psychopathological approach, was the initiation of a psychological approach to the management of these disorders (psychotherapy, antidepressants and more recently stress-management) that has been beneficial to some individuals suffering from these disorders. The effectiveness of psychological management reinforces the notion that psychological disturbance is an important component of these disorders for many patients with IBS/FD. *However, the precise role of psychosocial factors in IBS/FD remains contentious.* While research continues to report high levels of psychosocial disturbance in these disorders, attempts to distinguish between cause and effect remain elusive. Alternative propositions which warrant attention, suggest a) that psychological distress in these disorders is secondary to a painful and disruptive illness, and b) that psychological distress in patient samples is not representative of individuals with these disorders in the community. It is thought that psychological distress induces sensitivity to

somatic symptoms which prompts some individuals to seek health care. Factors critical to resolving these issues include determining:

1. whether psychological disturbance precedes the onset and/or exacerbation of IBS/FD - an issue of the temporal association and its reliability.
2. whether the prevalence of psychiatric disturbance in patients and non-patients with IBS/FD is significantly greater than the norms of the general population and patient groups with similar painful and disruptive organic GI disorders (eg IBS versus inflammatory bowel disease and FD versus and peptic ulcer disease) - a matter of concern is whether functional GI symptoms coexist with the organic symptoms in some of the control patient samples.
3. whether distress levels are similar in individuals with IBS/FD irrespective of the decision to seek professional help.
4. whether the severity of IBS/FD symptoms correspond in a linear manner with the severity of the psychological disturbance.
5. whether various aspects of the psychological disturbance predict subsequent changes in symptom severity in longitudinal studies using sophisticated methodologies.

A dramatic increase since 1990 in the number of well designed patient and community studies has considerably expanded the information now available to allow a more comprehensive evaluation of these issues even though the primary issue of a causal relation remains unresolved. It is somewhat intriguing that despite the current prominence of the biopsychosocial model as an explanatory paradigm for interrelations between mind and gut in IBS/FD little credence is given to the possibility that the alternative propositions need not exclude a 'causal' role for psychosocial disturbance. It is not inconceivable

that the psychosocial disturbance at consultation represents in part the psychosocial trigger of a recent onset, recurrence or exacerbation, in part the effects on emotional well-being of a painful and disruptive disorder which in turn may influence the decision to seek professional help in the same manner that it may influence the seeking of care in other patient groups. That is, the alternate propositions need not exclude a 'causal' association. It is the task of research groups using appropriate methodologies to demonstrate that psychosocial disturbance cannot be dismissed as a potential factor, or cofactor with as yet unknown physiological factors, in the etiology of the majority of cases of IBS/FD.

### **Psychiatric illness**

As indicated above the high prevalence of psychological symptoms in IBS and FD samples has given rise to proposed etiologic links with psychiatric illness in general (Mishra et al, 1984; Crean et al, 1982), or more specific associations with *depression* (Lopez, 1972; Drossman et al, 1982; Harvey et al, 1983; Mishra et al, 1984; Clouse, 1988), *anxiety disorders* (Drossman et al, 1982; Mishra et al, 1984; Clouse, 1988), *somatization of affect* (e.g. Whitehead et al, 1980), *hypochondriasis* (Hill & Blendis, 1967; Magni et al, 1987a) and *abnormal illness behaviour* (Whitehead et al, 1982). Although psychiatric status is always evaluated on the basis of clinical interview, some reports of psychiatric illness which are noted in some samples but not others (and are not dealt with here) include: hysterical mechanisms (21%) (Gomez & Dally, 1977); psychogenic pain syndromes (Gomez & Dally, 1977; Drossman et al, 1988; Mishra et al, 1984; Varis, 1987), adjustment disorder with mixed emotional features (3%) (Magni et al, 1987a); anger and denial (9%) (Bergernon & Monto, 1985), inadequate

dependency (28%) (Bergernon & Monto,1985), and unrecognised alcoholism (15%) (Gomez & Dally, 1977). The reliability of some of these classifications is diminished somewhat by idiosyncratic determinations, clinical judgement not based on standard criteria, and only partial use of otherwise reliable diagnostic criteria (Creed & Guthrie, 1987). That is, in some studies the full diagnostic criteria of the classification manuals, the International Classification of Diseases (e.g. ICD) (World Health Organisation, 1977) and The Diagnostic and Statistical Manual of Mental Disorders (e.g. DSM-III) (American Psychiatric Association, 1980), upon which psychiatric 'caseness' as well as differential diagnosis is based, have not been fully utilised. Others report only a subgroup of primary psychiatric disorders, current and lifetime diagnoses are not always clearly differentiated, and control group selection is sometimes inadequate (Walker et al, 1990; Creed & Guthrie, 1987; Talley et al, 1993). The following discussion is based on studies where the methodology is adequate. Research in this area derives from both psychiatric interview and psychometric testing.

Controlled studies using standardized psychiatric interviews consistently indicate that psychopathology in IBS/FD is high (Appendices G and H list the research groups, the methods they have used, and their findings for current and lifetime psychiatric illness respectively). Overall these data indicate that significantly more patients with IBS/FD have attracted a psychiatric diagnosis than patients with an organic GI disease and healthy control subjects. The median prevalence of current psychiatric illness in IBS/FD is 53% (range, 20 to 87%) which is markedly higher than in both organic GI patients (14%), healthy control subjects (18%) and community norms (see Oakley-Browne et al, 1989). It is noted that with the exception of one study (Dinan et al, 1991) these differences are significant. Two studies have attempted a more etiologic approach. Ford and

his colleagues (1987) assessed the prevalence of psychiatric disorder prior to onset/exacerbation of FGID (42%) and Toner's research group (1990a) assessed the prevalence of psychiatric disorders in IBS during the previous 12 months (59%). In support of the 'causal' proposition, psychiatric illness was significantly more common in FGID and IBS during the previous 12 months than in patients with organic GI disorders and healthy control subjects (6 and 14% respectively). Psychiatric illness is also evaluated over a lifetime. Based on the proposition that a history of psychiatric illness may function as a precursor to (or a vulnerability factor for) IBS/FD, and well supported by research, evaluations of lifetime psychopathology yield estimates of between 50 and 94% in patient samples with IBS/FD (see Appendix H). Moreover, the percentage with a history of psychopathology is significantly greater than in patients with organic GI disorders (range 19 to 30%) (Walker et al, 1990; Talley et al, 1993) and healthy individuals (range 21 to 34%) (Toner et al, 1990a; Talley et al, 1993; Jarrett et al, 1998). The most common psychiatric diagnoses (current and lifetime) in individuals with IBS/FD are depression, generalized anxiety disorder, and somatization. Suggestions that other conditions such as panic disorder may have a special role in IBS (Lydiard et al, 1986) have not been supported (Walker et al, 1992; Talley et al, 1993; Lydiard et al, 1994; Jarrett et al, 1998).

While psychiatric interview methods indicate that psychological disturbance satisfies caseness in approximately half the patients with IBS/FD (MacDonald & Bouchier, 1980; Ford et al, 1987, Colgan et al, 1988; Guthrie et al, 1990; Blanchard et al, 1990), psychometric measures reveal that many of the remainder have sub-clinical levels of psychological distress. In particular, psychometric assessments reveal a wide range of levels of psychological distress in IBS/FD samples in terms of both the type and the severity of comorbid

psychological symptoms. Overall, the findings from both methods suggest that high prevalence rates of psychiatric illness in groups of individuals with IBS/FD reflect widespread psychological distress in patient groups in general, and severe psychological distress for some individuals in particular.

Of interest also, are recent findings which help to clarify the issue of seeking health care in IBS. Jarrett and colleagues (1998) are the first to show that women with IBS who have not consulted have a similar prevalence of at least one episode of psychopathology (59%) as IBS women who have consulted (66%), both are significantly greater than in healthy women (34%). Similarly, scores on a global measure of psychological disturbance (SCL-90R) also demonstrate that both groups of IBS women are significantly more distressed than women from the general community. That is, at least for women, comorbid psychological distress is strongly associated with IBS per se irrespective of consultation choices.

In summary, there is little difference in the number of individuals with psychological morbidity in IBS/FD irrespective of their decision to consult (or not to consult), and little difference between levels of psychopathology whether the data is derived from psychiatric interview or psychometric testing. Each method suggests that psychopathology (current or lifetime) is more common in patients with the most severe IBS/FD symptoms (for example, patients in special treatment programs (Lydiard et al, 1993)); patients seeking opinion and/or investigation (outpatients) and non-patients with IBS appear to be intermediate between the severe IBS/FD patients and healthy individuals in the community. The variable intensity of psychological symptoms in IBS/FD samples suggests heterogeneity within groups of individuals with these disorders - for example, in almost all groups, psychological symptoms are either absent or at a subclinical level for some individuals. Overall however, the contrast between the presence

and severity of psychological symptoms within IBS/FD patient (and non-patient) groups compared with patients with organic GI disease and healthy subjects suggests that psychological distress is an important component of these disorders for the majority of patients, (perhaps especially for women) and is not simply an artefact of help seeking behaviour. In the following, the literature on the most frequently diagnosed psychiatric disorders - depression, anxiety and somatization - is evaluated with particular emphasis on the potential of one or more of these factors to have causal relations with the onset, exacerbation or course of these disorders.

### **Depression**

The prevalence of major depression in patients with FGID varies somewhat according to diagnostic criteria, assessment methods, and sample characteristics. A psychiatric diagnosis of a primary depressive illness based on clinical judgement alone yields highly variable findings, with prevalence rates ranging from 38% (Gomez & Dally, 1977) to 96% (Latimer et al, 1981). In contrast, clinical interview studies using research diagnostic criteria for psychiatric disorders report that 10 to 27% of patients with IBS attract a diagnosis of major depression (Dinan et al, 1991; Wender & Kalm, 1983) while a study using DSM-III flow sheets found that only 3% of patients with essential dyspepsia met requirements for a chronic depressive disorder (Magni et al, 1987a).

Psychometric measures yield prevalence rates of major depression (11-21%) remarkably similar to those based on the standard psychiatric diagnostic criteria. Depressive symptoms are widely variable within FGID samples, scores ranging from zero to levels suggestive of a depressive illness of probable clinical significance. A typical distribution pattern for depressive symptoms in FGID

indicates that most patients (54%) are asymptomatic or have only very mild depressive symptoms, 27% have a disorder of moderate severity while 18% have symptoms within the severe range (Kingham & Dawson; 1985). By quantifying the affective disturbance in IBS/FD, Blanchard et al (1990) for example report that the mean scores of psychiatric patients are triple the scores of IBS patients in their study, suggesting a low-grade mood disturbance for most individuals with IBS that more closely resembles psychological distress, sadness, and unhappiness than a depressive illness of clinical significance. In short, only a small proportion of IBS/FD patients have severe depressive symptoms and most are either free of depression or suffer an affective disturbance of mild to moderate intensity.

The role of depression in IBS/FD remains unclear. In all comparisons of IBS/FD with general population samples, a major depressive illness (defined by either method) occurs no more frequently in patients with IBS/FD than in those without these disorders. However, on psychometric assessment patients with IBS and/or FD have significantly more frequent and/or more severe depressive symptoms than community controls. At least 11 controlled studies report significantly higher mean scores for IBS (e.g. Whitehead et al, 1980, Richter et al, 1986; Drossman et al, 1988, Nylin et al, 1993) and several studies for FD (Talley et al, 1986; Magni et al, 1988 and Bennett et al, 1991; Haug et al, 1994b), than for community control subjects. Higher levels failed to reach significance in one study only (Kumar et al, 1990).

The status of depression in IBS/FD relative to other patient groups is more controversial. A higher mean level of depression was a significant feature of IBS compared to patients with nutcracker oesophagus (Richter et al, 1986), inflammatory bowel disease (Blanchard et al, 1990), organic GI disorders (Gomborone et al, 1995b) and minor surgical problems (Rose et al, 1986) but

levels were similar to a mixed functional and organic GI group (Welch et al, 1984) and to two mixed organic GI groups (Bleijenberg & Fennis, 1989; Kumar et al, 1990). Similarly, a higher mean level of depression was a significant feature of FD compared to patients with duodenal ulcer disease (Haug et al, 1994b) but in other studies FD was similar to peptic ulcer disease (Langeluddecke et al, 1990) and essential dyspepsia and functional abdominal pain to duodenal ulcer disease (Talley et al, 1986; Jorgensen et al, 1996). Although mean levels of depression are generally highest in IBS/FD groups, intermediate in organic GI groups, and lowest in the general population, differences between elevated depressive symptoms in patients with duodenal ulcer disease (Talley et al, 1986; Jorgensen et al, 1996) and inflammatory bowel disease (Schwarz et al, 1993) were significantly higher than in the general population. Overall it seems that a mean level of depression, that is lower in IBS/FD than in patients with a major depressive disorder (Gomborone et al, 1993; Gomborone et al, 1995b), coexists with a number of gastrointestinal conditions, perhaps especially with IBS and FD.

While a causal relation between depressive symptoms and the onset of IBS/FD has not been demonstrated, there is substantial evidence that depressive symptoms predate (or develop concurrently with) IBS/FD rather than develop as a consequence of distressing GI symptoms.

A major depressive syndrome, in which IBS/FD could be considered secondary (Latimer et al, 1979a), may account for symptoms in only a small proportion of these patients. Depressive symptoms often predate the onset or exacerbation of IBS/FD symptoms in patients with a major depressive disorder. Dewsnap and colleagues, revealed that most patients with acute psychiatric disorders (90% with depression, 10% an anxiety disorder) and concurrent IBS, report an exacerbation of their IBS symptoms after the onset of depression

whether they had consulted (69%), or not consulted (55%), for their IBS symptoms (Dewsnap et al, 1996). Also consistent with the proposition that depression predates the onset or exacerbation of IBS/FD, a lifetime psychiatric diagnosis of depression, (potentially more 'causal' than current depression), is far more differentiating of IBS relative to inflammatory bowel disease (Walker et al, 1990) and healthy community subjects (Toner et al, 1990a; Talley et al, 1995b) than the presence of a current depressive illness.

A proposition that is gaining in currency is that both depression and FGID are provoked by particular types of life stress (e.g. loss events, sexual abuse) that have occurred recently and/or early in life and may act as precursors for the future development of FGID and/or depressive disorder. Gomez (1977) reports an excess of bereavements in the preceding 12 months among patients with chronic abdominal pain and concurrent depression, while several authors (Chaudhary & Truelove, 1962; MacDonald & Bouchier, 1980) report that functional GI symptoms were associated with 'nerves', 'depression' unhappy childhood, early parental loss and early separations during childhood. Consistent with the above, effective treatment of a major depressive illness in patients with FGID has been found to ameliorate their GI symptoms, but antidepressant medication has not proved effective as a general treatment (Hill & Blendis, 1967; Gomez & Dally, 1977; Magni et al, 1987b).

While a depressed mood state secondary to abdominal pain and disturbed bowel function that is chronic, often unpredictable, and for which no cause can be found, may affect the subjective experience of FGID symptoms and/or enhance a depressed mood state (Kramlinger et al, 1983), it is unlikely to explain the severe depression found in some individuals with IBS/FD. Similarly, there is diminishing support for the suggestion that depression levels in patients with IBS/FD merely

reflect self-selection processes. In Blanchard et al's study (1990) for example, patients with inflammatory bowel disease were psychologically less distressed (less anxious and depressed) than IBS patients and yet both had sought treatment for chronic, painful and distressing bowel symptoms. It seems illogical to assume that IBS patients consult because they are psychologically distressed but patients with inflammatory bowel disease consult for other reasons. Besides, issues relevant to type, chronicity and severity of IBS symptoms and their consequences on life style are at least equally likely to provoke consultations.

Given the heterogeneous pattern of depression in IBS/FD - severe in some, but mild to moderate or absent in the majority - and the failure of studies to assess the on-going association of depression to subsequent IBS symptoms over time, the role of depression remains unclear.

### **Anxiety**

Anxiety disorders in IBS/FD are strongly linked by patterns of association similar to those for depression. In clinical interview studies, using research diagnostic criteria for psychiatric disorders, the prevalence of anxiety disorders varies widely, from 6 to 40% for IBS/FGID (Dinan et al, 1991; Blanchard et al, 1990) and from 5 to 67% for FD (Mishra et al, 1984; Magni et al, 1987b). A comparison of prevalence rates based on psychiatric and psychometric criteria once again shows them to be similar, suggesting on average approximately 26% of patients with IBS and 37% of patients with FD to have at least one anxiety disorder of clinical significance. Chronic tension is frequently present in patients with chronic abdominal pain, and an excess of family conflicts seems to be an important feature of those with these tension states (Gomez & Dally, 1977). Although current anxiety disorders occur more frequently in patients with IBS

than in non-clinical samples, these differences did not reach significance in any study. In contrast, a diagnosis of anxiety disorder during the previous year (Toner et al, 1990a) or a lifetime diagnosis of generalized anxiety disorder (Jarrett et al, 1998) occurs significantly more frequently in patients with IBS than in community control subjects while the presence of one or more phobia over a lifetime also may be more likely in IBS than in inflammatory bowel disease (Walker et al, 1990).

State anxiety in IBS/FD has consistently been found to be high when compared with either community controls or general population norms. Almost without exception, elevated anxiety states exceed community levels in at least 17 studies of IBS (e.g. Blanchard et al, 1990; Kumar et al, 1990; Heaton et al, 1991; Sullivan et al, 1995), four of FD (Talley et al, 1986; Magni et al, 1988; Bennett et al, 1991) and one study of functional abdominal pain (Jorgensen et al, 1996). High levels in comparison with community controls failed to reach significance in one study only (Magni et al, 1988). It seems that mean scores for anxiety in FD are statistically similar to (although numerically lower than) those of psychiatric patients with 'psychoneurosis (Magni et al; 1985), but are considerably lower, even in treatment-seeking chronic IBS patients, than the norms for psychiatric patients with anxiety disorders (Blanchard et al, 1990). In comparisons between IBS and patient groups with specific organic GI disorders, levels of anxiety are significantly higher in IBS than in inflammatory bowel disease (Blanchard et al, 1990; Walker et al, 1990; Schwarz et al, 1993) and nutcracker oesophagus (Richter et al, 1986). It is unclear the extent to which differences in selection of patient and control samples may explain these contrasting results. Similar to the findings for depression, these levels do not differ from patients with mixed organic and non-organic GI disorders (Welch et al, 1984) or patients with mixed

organic GI disorders (Bleijenberg et al, 1989). Relations between anxiety and FD follow a similar pattern. In comparisons between FD and patient groups with specific organic GI disorders, levels of anxiety are significantly higher in FD than in organic GI (Magni et al, 1988), and peptic ulcer disease (Langeluddecke et al, 1990) but differences are equivocal with respect to duodenal ulcer disease - that is, state anxiety scores are higher in FD than in duodenal ulcer patients in one study (Haug et al, 1994b) but similar in patients with essential dyspepsia and duodenal ulcer in another (Talley et al, 1986).

While high levels of anxiety in these disorders may simply reflect 'patient' status, two recent studies suggest this may not be the case. In university students with IBS, trait anxiety scores did not differ between those who had sought medical care for their symptoms (mostly from a primary physician) and those who had not sought such care (Gick & Thompson, 1997). In the second study, state anxiety (and depression) scores were significantly higher in individuals with IBS, whether they had consulted or not consulted for their symptoms, than in individuals in the community without IBS (Jarrett et al, 1998). Although some uncertainties remain there is little doubt that individuals with IBS/FD are generally more anxious and generally distressed than individuals without these disorders. Whether anxiety and stress contribute to the development of IBS/FD symptoms is a separate issue.

More clearly defined links between anxiety and the onset and exacerbation of IBS/FD are emerging, which although not fully developed, suggest that anxiety, but not depression, is potentially 'causal' in these disorders. Several research findings contribute to this view:

- 1) Anxiety is the main psychiatric diagnosis for patients with IBS/FD (eg Latimer et al, 1981; Haug et al, 1994b), closely followed by somatization - the

presence of multiple non-gut symptoms - which are also considered to be stress-related (Kellner, 1991).

2) *Anxiety is a prominent feature of IBS/FD.* At least 14 studies attest to this. In one of the first studies to assess the relative importance of psychological factors in FD, our own data reveal that, of the factors significantly associated with FD (i.e. symptoms of anxiety and depression, neurotic and anxious tendencies, the use of less mature stress coping strategies and the absence of adequate intimate emotional support), the model of best fit ranked anxiety first (Bennett et al, 1991). A prospective community evaluation also supports the prominence of anxiety (Hochstrasser & Angst, 1996). In a ten year study of a representative cohort of 591 Swiss 20 year old adults, various anxiety (and depressive) disorders and various levels of severity of anxiety (and depression) were consistently associated with GI symptoms at each of four contact points. The most stable relation at each contact was between anxiety (not depression) and functional GI symptoms. Interestingly, these results are independent of treatment-seeking bias; they also suggest that even subthreshold levels of anxiety may influence functional GI function.

3) *Anxiety appears to be more relevant to functional GI symptoms in women.* In women patients with IBS, Hillman et al (1984) report that anxiety (not depression or somatization) correlate with the symptoms of IBS while in a mixed gender sample clinically significant anxiety in FD is more prominent than depression, particularly among women (Heatley et al, 1986). In a survey of bowel patterns and anxiety on 1264 health maintenance organisation members, Longstreth (1993) found that self-reported stress effects on bowel change and abdominal pain are related to age (younger more than older), gender (female more than male) and anxiety. The results indicate that more

women than men of all ages experience stress effects, and subjects who report either stress effect (bowel change or abdominal pain) have higher levels of state and trait anxiety than other people.

4) *Anxiety (more than depression or neuroticism) predates onset or exacerbation for most individuals with IBS/FD.* When asked, 82% of a sample of moderate to severe IBS patients report that psychiatric symptoms predated the appearance of functional GI symptoms (Walker et al, 1990). Most of these patients have a lifetime diagnosis of generalized anxiety disorder or panic disorder (61%), significantly more than those with inflammatory bowel disease (11%). The long duration of psychological distress prior to FGID symptom onset suggests that ongoing psychological distress might be an important precipitant of GI symptoms; it also discounts the notion that IBS is a somatic manifestation of acute psychiatric illness.

Several different lines of research provide more objective support. Worthy of note is a naturalistic study (Giacosa et al, 1987) which found a high correlation between anxiety and dyspepsia in a group of young conscripted soldiers. Dyspepsia symptoms were experienced by 64% of the anxious soldiers and only 9% of non-anxious soldiers following two to five months of compulsory military service. The possibility of a causal link between anxiety and FD is strengthened by the close temporal association of the development of anxiety and dyspepsia and the stress of military service. Only one study prospectively assessed the psychological predictors of onset of IBS. Gwee and colleagues (1996) documented the progress of 75 patients hospitalised for acute gastroenteritis for six months after the acute illness phase. Patients completed psychological measures and a bowel symptom questionnaire in hospital and again at three months and were subsequently allocated a

diagnosis of IBS-like or non-IBS-like based on their bowel symptom responses. Higher scores at entry on anxiety (and somatization) in particular but also depression and neuroticism, predicted the subsequent development of IBS symptoms for more than one third of the patients. In most of these patients IBS symptoms were still present at 6 months. A chronic anxiety state seem to be important to the onset of IBS-like symptomatology in the presence of enteric infection and intestinal inflammation; infectious diarrhoea alone did not explain the subsequent onset of IBS.

In summary, anxiety is a prominent feature of IBS/FD and is potentially more closely connected to the development of these disorders than other aspects of an emotionally distressed state.

### **Somatization**

The presence of multiple somatic non-gastrointestinal symptoms, such as fatigue, nervousness, insomnia, headaches, impotence, genito-urinary problems, backache and palpitations (Roberts, 1978; Whitehead et al, 1980; MacDonald & Bouchier, 1980; Whorwell et al, 1986b; Nyren et al, 1985a) is the most common condition other than psychological distress disorders to consistently coexist with IBS/FD symptoms in patients with these disorders. For patients with IBS, somatoform disorder was the most prominent psychiatric disorder after anxiety (Magni et al, 1988) and its lifetime prevalence rate was calculated at 17% in treatment-seeking patients with moderate to severe IBS in another (Lydiard et al, 1993). Current levels of somatization assessed by the Minnesota Multiphasic Personality Inventory suggest a prevalence of 16% in IBS (Bergernon & Monto, 1985). In most controlled studies, somatic (non-gut) symptoms are significantly more common in patients with FGID than in healthy control subjects

(Whitehead et al, 1980; Welch et al, 1984; Talley et al, 1991b; Haug et al, 1994b; Schwarz et al, 1993; Talley et al, 1995b and Jorgensen et al, 1996), non-patients with some bowel symptoms (Talley et al, 1995b) and most homogeneous organic GI groups - for example, duodenal ulcer disease (Haug et al, 1994b; Jorgensen et al, 1996), peptic ulcer disease (Whitehead et al, 1982), inflammatory bowel disease (Walker et al, 1990; Schwarz et al, 1993) and patients with either gallstone or urinary calculi (Jorgensen et al, 1996) while Magni and colleagues (1988), report a tendency for some essential dyspepsia patients to be more prone to somatic symptoms in response to moderate distress than organic dyspepsia patients. Once again, differences were not found when IBS/FD were compared with patient groups comprising mixed organic and/or functional GI symptoms (Smith et al, 1990; Welch et al, 1984; Talley & Piper, 1986b; Kumar et al, 1990 and Talley et al, 1991b).

In support of a strong association between non-gut and gut somatic symptoms that is unrelated to self-selection, the somatization scores are similar in consulters and non-consulters with IBS, and significantly higher than those of healthy community subjects (Jarrett et al, 1998). In terms of overall severity, somatic complaints (as was noted in relation to anxiety and/or depression) are moderate in IBS/FD. In comparison to patients with a psychiatric diagnosis of somatoform disorder somatization scores in patients with functional and organic GI disorders are significantly lower (Talley et al 1991b), placing IBS/FD in a position intermediate between patients with somatoform disorders and healthy control subjects.

While it is clear there is a strong tendency for the symptoms of somatic (non-gut) conditions to coexist with GI symptoms in IBS/FD, there is little direct evidence that psychological distress (anxiety, depression) underlies this

tendency as implied by the use of the terms ‘somatization of affect’ (Whitehead et al, 1980) and ‘somatic anxiety’ (Kumar et al, 1990). Very few studies have examined interrelations between psychological distress (anxiety, depression) and the presence and severity of somatic (non-gut) symptoms in IBS/FD. Links have been found between both neuroticism and psychological morbidity and the severity of somatic (non-gut) symptoms (Talley et al, 1995), between somatic symptoms and FGID symptom type (in particular defecation) and severity (Talley et al, 1995), and between anxiety (but not somatization or depression) and the severity of IBS symptoms (Hillman et al, 1984). Also, although the severity of anxiety and depression scores is associated with the severity of somatic and IBS symptoms combined (Tollefson et al, 1991), psychiatric illness per se is not associated with the severity of somatic and non-colonic (eg FD) symptoms combined (Whorwell et al, 1986a). While these findings are inconclusive concerning the interrelatedness of these factors, an additional association, that is, between seasonal effects on mood state (also sleep and dietary patterns) and changes in IBS and somatic symptoms (Talley et al, 1995b), adds another dimension to the complexity of relations between psychological distress, somatic and FGID disturbances.

Some researchers regard the high prevalence of depressive, anxiety and somatic symptoms in FD as part of a more diffuse psychoneurotic condition (eg Giacosa et al, 1987; Magni et al, 1987a; Magni et al, 1985). Others propose that IBS (and somatic non-gut) symptoms may be just one facet of a more general condition of illness behaviour (Nyhlin et al, 1993). Whorwell and colleagues suggest that the concurrence of an irritable gut in FGID with altered smooth-muscle function in other organs (e.g. urinary bladder (Whorwell et al, 1986b) and gallbladder (Kellow & Phillips, 1987)) may in fact represent a generalized

underlying disorder of smooth muscle (Whorwell et al, 1986a; Whorwell et al, 1986b). Although electrophysiological abnormalities are increasingly reported in FD patients (You et al, 1980), there is no direct evidence of a link between stress and the development of abnormal gastric tone. However, the significant correlation of symptoms that are characteristic of depression (e.g. fatigue, insomnia, impotence) and of anxiety (nervousness, palpitations) with those associated with smooth muscle abnormalities provides some circumstantial support for such this suggestion. Alternatively, emotions may simply precipitate or aggravate somatic symptoms arising from subtle neurophysiological deficits not yet elucidated (Meares et al, 1985; Kellner, 1991). While each proposition is based on the assumption of a strong association between emotional distress and the presence of multiple non-gastrointestinal symptoms in FGID, there is insufficient information at present to support or discount any particular view. It is clear that further research is required to fully understand the relevance of somatic symptoms to IBS/FD.

### **Summary**

Psychological morbidity is widespread in patients and non-patients with IBS and with FD, significantly more so than in patients with organic GI diseases and people without these disorders. This is a highly consistent finding for both current (Appendix G) and lifetime (Appendix H) psychiatric disorders, and from data derived from both interview and psychometric techniques. While on average, symptom levels for anxiety, depression and somatization are significantly less than in psychiatric patients, approximately half have symptoms sufficiently severe to attract a clinical diagnosis and most have had an episode of one or more of these disorders in the past. The severity of psychological symptoms in IBS/FD,

which range from asymptomatic, to moderate, to clinically severe, have been described variously as an anxious-depressed state or more commonly, psychological distress. Overall, studies indicate that IBS develops in the presence of a highly distressed state. A recent study (Gwee et al, 1996) specifies that the prospective development of IBS occurs (following infectious diarrhoea) *only* in those with a highly anxious and distressed state. Another shows that psychological distress is just as significant a feature of women with IBS who have not consulted as those who have (Jarrett et al, 1998). This, and other evidence that onset or exacerbation of IBS follows periods of severe emotional distress provides considerable support for the stress hypothesis, particularly when, as in Gwee's study, the psychological factor is a primary factor or cofactor of IBS onset, and the study is free of care-seeking bias. The credibility of claims that high levels of psychological distress in symptomatic IBS samples simply reflect patient status is diminished by these findings.

Anxiety disorders, including the presence of somatic (non-gut) symptoms are a primary component of the psychological distress that appears to have such a prominent role in IBS/FD. They are certainly the most frequently diagnosed disorders and have the clearest relation with onset and exacerbation. Depressive symptoms are less consistently present and their role less clear. Although the early belief that IBS is a manifestation of an affective disorder has been soundly discounted, the presence of depressive symptoms and their effects on clinical recovery are important issues. A comprehensive investigation of the relation of depression to FGID symptom intensity over time is one way this study can examine further its role in these disorders.

## 1.2.2 PERSONALITY, COPING AND IBS/FD

### **Neuroticism / Trait Anxiety**

Personality traits, particularly of a neurotic kind, have been proposed as important predisposing factors in FGID. Anecdotal evidence suggests a predisposition to exaggerated reactivity or lability (with anxious, hysterical, obsessional and/or hypochondriacal tendencies), with patients with IBS/FD having been described as sensitive, nervous, highly strung (Kingham & Dawson, 1985), tense (Lagarde & Spiro, 1984), and vigilant (Nyren et al, 1985a), as being very concerned about the seriousness of their symptoms (Jones & Lydeard, 1989), or as having rigid perfectionistic attitudes (Hill & Blendis, 1967). There is some empirical support for this view.

On average, *trait anxiety* is elevated in all studies of patients with FD (Talley et al, 1986; Bennett et al, 1991; Haug et al, 1994b), and IBS (Latimer et al, 1981; Smith et al, 1990; Schwarz et al, 1993; Gick et al, 1997), and are significantly higher than in community controls. Chronic tension and hostility are also generally higher than in individuals without chronic abdominal pain (Gomez & Dally, 1977), peptic ulcer disease (Langeluddecke et al, 1990) and healthy controls (Whitehead et al, 1980; Jarrett et al, 1998). The similarity of the mean trait anxiety scores of both patients and non-patients with IBS, both significantly higher than in IBS-free subjects from the same university student population (Gick et al, 1997), strengthens the specificity of trait anxiety to IBS. There is some evidence that they also exceed the levels observed in certain patient groups e.g. inflammatory bowel disease (Smith et al, 1990) and duodenal ulcer disease (Haug et al, 1994b), but findings in this area are by no means consistent (Schwarz et al, 1993) and statistical significance in some study populations may depend on whether age and gender are controlled (Langeluddecke, 1990).

As with anxiety, mean *neuroticism* scores are elevated in IBS patient and community samples (Talley et al, 1998) and in patients with FD compared with levels in community control subjects (Latimer et al, 1981; Talley et al, 1998) matched for age, sex and social class (Talley et al, 1986; Bennett et al, 1991) and general population norms (Palmer et al, 1974; Hill & Blendis, 1967; Roberts et al, 1978). While there is some evidence that neuroticism in IBS and FD is significantly higher than for ulcer patients (Roberts et al, 1978; Palmer et al, 1974), patients with ulcerative colitis (Esler & Goulston, 1973) and general medical inpatient groups (Wilson et al, 1989; Esler & Goulston, 1973), this is counterbalanced by reports of neuroticism levels comparable with other patient groups including peptic ulcer disease and other gastrointestinal disorders (Langeluddecke et al, 1990; Talley et al, 1986; Gomez & Dally, 1977; Bleijenberg & Fennis, 1989). Overall, levels of trait anxiety and neuroticism are high in patient and community samples with IBS. In both IBS and FD, levels are generally higher than in other patient groups, and significantly higher than in the general population. While group comparisons reveal levels of trait anxiety and neuroticism to be high in patient and nonpatient IBS populations, they reveal little about the effects of these personality traits on the development or exacerbation of IBS. It is unclear also, the extent to which trait anxiety and neuroticism scores on measures such as the EPI or STAI reflect distressing circumstances as well as innate/genetic tendencies. According to Creed and Guthrie (1987), elevated neuroticism scores may reflect a history of prolonged physical or psychological illness or, as a recent community study suggests, child sexual abuse may induce the expression of neuroticism which in turn leads to the subsequent onset of IBS (Talley et al, 1998). The proposition that high levels of neuroticism (with or without distressing circumstances) predict an unfavourable prognosis for

individuals with IBS, is supported longitudinally by the studies of Chaudhary and Truelove (1962) and Bleijenberg and Fennis (1989). People with IBS and a tendency to anxious responses also demonstrate a closer relation between stress effects and alterations in bowel pattern and abdominal pain. In a study of 1264 health maintenance organisation (HMO) members, Longstreth (1993) found high levels of state and trait anxiety to be associated with the subject's observation that alterations in their bowel pattern and abdominal pain were stress-related, women noting these effects more than men. In their innovative study, Esler and Goulston (1973) found an association between high levels of trait anxiety and neuroticism and high levels of stressor-provoked alterations in urinary norepinephrine excretions in diarrhoea-predominant IBS, but not in pain-predominant IBS or in pain-predominant ulcerative colitis. While their findings suggest that neurotic tendencies enhance stress responses which in turn may provoke a particular type of IBS syndrome, Esler and Goulston (1973) are quick to note that the anxiety scores of some individuals even within the diarrhoea-predominant subgroup fall well within the normal range. This observation suggests that neuroticism alone is insufficient to produce these effects. It remains to be determined, therefore, whether neuroticism alone or in combination with distressing circumstances influences the clinical outcome in IBS.

Despite the popularity of the notion, community studies do not suggest that anxious, neurotic individuals with IBS are more likely to consult than those without these tendencies. In an Australian study, Talley et al (1997) found that seeking health care for IBS was associated with the severity and duration of pain but not with neuroticism, psychological morbidity, or an abuse history. Similarly, in Canadian university students with IBS, Gick et al (1997) found that trait anxiety scores on the STAI did not differ between students who decided to seek

help and those who did not. While the issue of personality and consultation remains inconclusive, these studies suggest that if anxious neurotic tendencies do influence consultation behaviour, the effects may be smaller and more subtle than previously thought.

In summary, although much research has sought and not found a personality that is characteristic of IBS, it has shown higher levels of neuroticism in groups of individuals with IBS that is unrelated to the decision to consult. Higher levels of neuroticism in IBS have been linked with specific changes in IBS symptoms and with stress-related effects on symptom severity that are observed more frequently by women than men. Preliminary findings suggest that neuroticism and stressful circumstances may have more effect on the course of IBS than neuroticism alone. High levels of neuroticism also may predispose to an unfavourable outcome long-term, but the evidence is far from conclusive.

### **Introversion**

Scores on the Eysenck Extraversion-Introversion Scales invariably indicate that patients with IBS and FD are more introverted than a variety of other 'healthy' and patient groups. Dinan et al (1991) reports scores to be in the extreme range for 60% of IBS patients, and Langeluddecke et al (1990) for 29% of FD patients, significantly more than in patients with peptic ulcer disease (9% and 13% respectively). Statistical significance is highly variable however with introversion scores differing from healthy controls in some studies (Latimer et al, 1981; Schwarz et al, 1993) but not in others (Talley et al, 1986; Bennett et al, 1991). They differed significantly from patients with peptic ulcer disease (Langeluddecke et al, 1990; Dinan et al, 1991), general medical conditions (Esler & Goulston, 1973) and neurotic disorders (Latimer et al, 1981; Palmer et al, 1974)

but not in comparison with duodenal ulcer disease (Talley et al, 1986). The effects of introversion on the course of functional GI symptoms has received little attention. Gwee et al (1996) included the Eysenck Personality Inventory in their assessment of the effects of psychological factors on GI symptomatology following an acute episode of infectious diarrhoea. Unlike state anxiety and other stress-related variables, introversion does not differ between those who subsequently develop IBS for the first time, and those whose bowel function returns to normal.

Overall, the results suggest a clear trend towards greater introversion in patients with IBS/FD but its role in IBS/FD remains unclear. Issues such as whether introversion combines with other psychological factors to determine functional rather than organic GI disorder and whether introversion influences the course of functional GI disorders long-term, have not been addressed.

### **Illness behaviour, illness disruption and hypochondriasis**

There is consistent evidence that some IBS/FD patients are concerned that their GI symptoms may reflect a serious and perhaps life-threatening disease (Hill & Blendis, 1967; Magni et al, 1987a; Jones, 1989). Perceptions as to the seriousness of dyspeptic symptoms is an important factor in influencing the decision to consult medical personnel (Jones, 1989). This concern is understandable given evidence that “consulting patients have frequently had experience of abdominal malignancy in friends or family” (Jones, 1989; p895). Similarly, Jones (1989) and Hill & Blendis (1967), report that the parents of many FD patients had suffered abdominal pain, and this was more prevalent than for those with organic disease. While these concerns may not constitute hypochondriasis they do fall within the broad category of illness behaviour

(Mechanic, 1961). It is not unreasonable to expect that given the 'non-organic' or 'functional' status of these chronic and disruptive disorders (especially IBS), various aspects of abnormal illness behaviour (Pilowsky, 1975) might become manifest, perhaps even moreso in research samples (i.e. in presenters) than in the community. However, the limited evidence available fails to support the proposition for FD patients as a group. Essential dyspepsia patients do not display excessive illness behaviour; they are no more likely to take days off work, or visit their GP more frequently than peptic ulcer and biliary pain patients (Talley & Piper, 1986b), and if they do, it is to seek help for other symptoms, particularly those of a musculo-skeletal nature (Nyren et al,1985a).

Research is more supportive of excessive illness behaviour in IBS groups. Health worries, illness disruption, health-related phobias and hypochondriasis, each assessed on more than one psychometric subscale, are greater in IBS patients than in any other patient or healthy group. Two research teams, Drossman et al (1988) using Pilowsky's Illness Behaviour Questionnaire (IBQ) and the MMPI, and Gomborone et al (1995b) using Kellner's Illness Attitude Scale (IAS), found that patients with IBS report significantly more *health worries* than 'healthy' individuals (Drossman et al, 1988) and endorse more *worry about illness* than patients with organic GI disorders (Gomborone et al, 1995b). IBS patients also report more severe *effects of symptoms* than patients with organic GI disorders (Gomborone et al, 1995b) and more *illness disruption* than IBS non-patients and healthy individuals (Drossman et al, 1988). It is tempting to hypothesise for some IBS patients, a connection between increased health worries, the severity and disruptive effects of a particular GI symptomatology and the decision to consult - especially if the person's peculiar life-style requirements and current emotional state are considered. Certainly, the severity of symptoms

alone does not seem to account for the decision to consult (Farthing, 1995) although pain severity, which correlates with hypochondriasis in patients with essential dyspepsia, IBS and organic GI (Talley et al, 1990a), may indirectly influence consultation. Similarly in patients with functional upper abdominal pain, those with a psychiatric disorder (primarily anxiety or depression) demonstrate more illness behaviour, have more abdominal symptoms and their pain is both more severe and more persistent than in patients with organic GI disease and those with functional GI disease and no psychiatric illness (Colgan et al, 1988).

The overall poorer health status of patients with FGID (for example in comparison to those with an organic GI diagnosis) is potentially much more likely to explain both increased levels of health-related worries in individuals with IBS and their decision to consult. In a recent study of 239 tertiary-care patients (92 with FGID, 147 with organic GI disorders), Drossman et al (1996(b)) found that patients with FGID (almost half with IBS) had poorer *health status* than patients with a structural organic diagnosis. The functional diagnosis was associated with greater pain severity, more psychological distress and poorer daily function. These researchers also found that independent of a functional diagnosis, an abuse history significantly contributed to greater pain severity, more days in bed, more psychological distress and poorer daily function. In particular, their study illustrates the complexity of psychosocial and functional gut interrelations over time - also, the wide range of issues that need to be considered when attempting to determine the psychophysiological etiology of FGID. The variable contribution of psychological, gender and physiological factors to etiology and to consultation in these disorder is further illustrated by the prominence of the hypochondriacal signs of “anxiety and uneasiness” (more prominent in males) in patients with *H*

*pylori* negative FD compared with FD patients with a positive *H pylori* finding (Andersson et al, 1994). That is, IBS samples are marked by considerable within-group differences in terms of the relative contribution of psychological and physiological factors to IBS.

Hypochondriasis attracts a psychiatric diagnosis in only 6 to 7% of IBS and FD patients (Lydiard et al, 1993; Magni et al, 1987b). Psychometric measures of abnormal illness behaviour identify a cluster of factors that are most specific to IBS. These almost exclusively include hypochondriacal illness-related fears, beliefs and attitudes assessed as *hypochondriacal beliefs*, *bodily preoccupation*, *disease phobia* (Gomborone et al, 1995b) and *hypochondriasis* (Drossman et al, 1996). *Illness disruption* is the only non-hypochondriasis factor (Drossman et al, 1996). Importantly, the relation of these factors to IBS is independent of levels of depression (Gomborone et al, 1995b). These factors are also highly specific to IBS non-patients as well as IBS patients, both having significantly different attitudes to illness compared with symptom-free controls; the position of non-patients being between IBS patients and healthy community control subjects (Farthing, 1995). IBS has also been linked to a peculiar confirmatory bias for negative material that is also independent of depression (Gomborone et al, 1993) and to dysfunctional attributions which if not dealt with early in the consultation process may result in an increase in somatic attributions (the belief that a somatic cause for symptoms has been missed) and a subsequent increase in primary care visits (van Dulmen et al, 1996).

To summarise, abnormal illness behaviour involving hypochondriacal fears, beliefs and dysfunctional attitudes is a prominent feature of IBS groups including community subjects with IBS. While within IBS samples the prevalence of clinical hypochondriasis is low, illness-related worries are not

uncommon (at least, prior to explanation and reassurance in the majority of cases). Excessive worries in individuals with IBS (for example in comparison to patients with an organic GI diagnosis) may be due to greater levels of pain severity and more persistent symptoms, psychological distress and poorer daily function - prominent and interrelated features in some patients with IBS (Drossman et al, 1996; Colgan et al, 1988). Importantly, certain aspects of abnormal illness behaviour in IBS are independent of depression - for example, abnormal illness attitudes and a heightened receptiveness to negative material. (Gomborone et al; 1993 & 1995b). However, dysfunctional attributions not allayed early in the consultation process are a major cause of subsequent consultations and further investigations (van Dulmen et al, 1996). Relations between illness worries, illness disruption, dysfunctional cognitions and behaviours, psychological distress, and inappropriate and/or repetitive seeking of health care, require further investigation in these functional GI disorders.

### **Suppression of emotions**

There is a popular belief that the tendency to suppress negative feelings such as anger, anxiety and unhappiness may be conducive to IBS/FD, presumably because they give rise to the somatic expression of 'stress' (Anderson, 1981; Lesser, 1981; Greer & Morris, 1975). Research is mixed in its support of this view. Global support is reported in two studies (Bennett et al, 1991; Nyhlin et al, 1993). The first used the Courtauld Emotional Control Scale (CECS) and found that overall FD patients tend to more frequently suppress anger, anxiety and unhappiness, at least at a conscious level, than age and sex matched healthy individuals (Bennett et al, 1991). Nyhlin and colleagues (1993) report a similar finding in patients with IBS using the affect inhibition subscale of the IBQ. In

addition to global effects, the first study indicates that although scores on all suppression of affect subscales are elevated in FD, only suppression of unhappiness (a sad, depressed mood) and suppression of anxiety differ significantly in FD patients compared with individuals from the general population; scores did not reach significance for anger (Bennett et al, 1991). In contrast, two studies which also used the CECS did not find that patients with essential dyspepsia or FD excessively suppress these unpleasant emotions when compared with matched community controls or duodenal ulcer (Talley et al, 1988a) or peptic ulcer disease patients (Langeluddecke et al, 1990). At odds with all of these findings is a report, based on impressions gained during an interview of functional and organic GI patients with upper abdominal pain (Stockton et al, 1985), that these patients are distinctive in the ways they deal with anger, many admitting to 'bottling up their anger' and some admitting that they 'never became angry'.

In summary, two studies using different measures suggest that patients with IBS and/or FD are more likely than the general population to conceal their feelings, but this is by no means a consistent finding. Suppression of unhappiness and anxiety may be more discriminating of the presence of IBS/FD than the suppression of anger, but interview data suggest it may be premature to dismiss suppression of anger as an important factor in these disorders. Also, type-A behaviour and hostility (reflecting a tendency to expressiveness of anger) appear to be more prevalent in a sample of women with IBS who also have experienced significantly more life stress than healthy matched controls over the previous 12 months (Dumitrascu & Granescu, 1996). Clearly the role of suppression / expression of unhappiness, anger, and anxiety in IBS/FD requires further exploration. Whether differences in expressiveness relate to differences in

physiological dysfunction is investigated for the first time in studies 3, 4, and 5 in relation to transit and sensory and/or motor dysfunction in IBS/FD patients.

### **Locus of control**

Measures of locus of control are designed to assess the extent to which a person believes that personal efforts, more than external factors can achieve a positive outcome. These beliefs fluctuate over time and circumstances. With respect to health, Craig & Brown, (1984) demonstrated that externality (the belief that other persons, circumstances, or chance are in control and personal efforts are generally futile) strongly predicts a poor outcome over time in terms of treatment failure and recurrence of the condition. Externality also predicts a poor short-term outcome (four to six weeks) for patients with either IBS and/or FD (Ryan, Dolphin, & Fielding, 1984). Lydeard and Jones (1989) administered a health locus of control measure to patient and community individuals with dyspepsia. Scores on this measure were similar in both groups although there was a slightly greater tendency to externality for those who consulted - that is, while differences were small they were theoretically in the expected direction. Entrenched low self-efficacy expectations such as those demonstrated in relation to externality may negatively influence symptom severity outcomes in patients with IBS or FD in the long-term.

### **Other personality traits**

Attempts to define a unique personality in IBS have been unsuccessful. Early descriptions of IBS groups summarised by Langeluddecke et al (1985) suggest they are compulsive, overly conscientious, neurotic, dependent, guilty,

and unassertive. A more recent study suggests gender differences, describing men with upper abdominal pain (some with organic GI disease) as diffident and listless and women as rather submissive and in need of their husband's support (Stockton et al, 1985). Controlled studies add obsessional traits and inward-directed hostility to the list, these traits being more frequently a feature of patients with IBS than of patients with inflammatory bowel disease (Kumar et al, 1990). Patients with FD on the other hand are reported to have significantly greater attachment to others. The presence of this factor distinguishes individuals with FD who consult from those who do not consult (Jonsson et al, 1994), and presumably from the norms of the general population. It is of particular interest that this trait now known to be genetically linked is also associated with the tendency to a parasympathetic (vagal) stress response (Uvnäs-Moberg et al, 1993). Relevant to the present context, greater attachment to others increases the likelihood of greater involvement in stress-related problems involving close others and increases vulnerability to emotional distress because of this. The relevance of personality to subsequent clinical outcomes in these disorders, especially relative to other psychosocial and demographic factors, is an issue that has not been researched using sophisticated prospective methodologies.

### **Coping style and emotional support**

A mature coping style (Andrews et al, 1989) and a close confiding relationship (Brown & Harris, 1978) represent two potential moderators of the impact of acute psychosocial distress. The role of coping difficulties, coping style and coping behaviour has been investigated by three research groups; the role of emotional support in one study only. The first links coping difficulties with abdominal bowel symptoms, the second associates coping style with the

presence of FD and the third suggests that coping behaviour has no effect on symptom severity long-term in patients with FGID.

Coping difficulties are reported by Johnsen and colleagues, (1986) to be associated with abdominal symptoms in 14,102 middle-aged community men and women, more than lifestyle, dietary or social variables together. The research group extends the investigation in community individuals to assess the relation of lifestyle, GI, sociodemographic and physical variables to a lifetime prevalence of FD or peptic ulcer disease (Johnsen et al,1988). Coping difficulties are associated with FD but not with peptic ulcer disease. FD is associated with psychological factors and social conditions including problems of coping, and peptic ulcer disease is associated with age, family history of peptic ulcer, body mass index and smoking. Mature coping such as the appropriate use of anticipation, humour, suppression and sublimation and good quality emotional support (especially intimate emotional support) are thought to modify the unpleasant emotions aroused whilst dealing with highly stressful circumstances. Only one study (Bennett et al, 1991) has attempted to determine the relative importance of these factors in patients with these disorders - that is, compared with the effects of a number of stress-related psychological, sociodemographic, and life stress variables that are known to be strongly associated with IBS/FD. It was our intention also to test the extent of their interaction with these other variables, in particular with personality and life stressor variables. We found these potential ‘buffers’ of the stressor experience to be either unavailable or inadequate in patients with FD. In comparison with their healthy control partner of the same age and sex, patients with FD use significantly fewer mature strategies and more maladaptive immature and neurotic strategies - also, they are far less likely to have an intimate emotional support partner, or if they do, the support is

inadequate or even negative in its impact. These findings suggest that during periods of severe stress some individuals with FD would be less able to modify negative emotional arousal and would be more prone therefore to greater and perhaps more prolonged stress responses. Unfortunately, it was not possible to test statistically for interactive effects between psychological, life stress and coping factors because of the overriding importance of the chronic stressor variables. The third study tested the effects of coping behaviour on long-term symptom severity in patients with FGID. The findings are negative. With the exception of neuroticism, coping behaviour (assessed on the Utrecht Coping List a standardized Dutch Scale), self esteem, and a number of psychological, sociodemographic and lifestyle factors do not predict the severity of FGID symptoms two years after initial assessment (Bleijenberg & Fennis, 1989).

### **Summary**

On average, patients with IBS/FD are more introverted, they have more neurotic and anxious personality traits, more abnormal illness behaviour and more hypochondriacal fears, beliefs and attitudes than patients with organic GI diseases and healthy individuals. They believe they have very little personal control over their current problems - instead, they attribute control to external factors such as other persons, circumstances or chance. They also tend to suppress negative emotions, in particular anxiety and unhappiness, and to deal with anger in 'distinctive' ways. However, they also experience more illness disruption, greater pain severity and poorer daily function than patients with organic GI diseases. Neurotic personality traits and dysfunctional cognitions may interact with the person's experience of these uncontrollable and disruptive disorders to enhance the intensity of functional symptoms over time; this has not been formally

investigated. It has been firmly established however, that many people with these disorders do not have neurotic tendencies. As Whitehead (1989) has noted, these personality differences are not found with sufficient frequency to serve as diagnostic markers of these disorders.

While a unique personality profile may not be demonstrable, it is quite possible that the psychological factors that are most consistently associated with IBS/FD (that is, those that are significant features of both patients and non-patients) may have special importance in these disorders. Of interest, these factors primarily include psychological morbidity (as mentioned earlier), but also certain personality, psychosocial and cognitive/attitudinal factors. Prominent among them is neuroticism (Talley et al, 1997), trait anxiety (Lydeard & Jones, 1989; Gick et al, 97), externality (Lydeard & Jones, 1989), hostility, interpersonal sensitivity, phobic anxiety, and obsessional compulsive tendencies (Jarrett et al, 1997). Of recent interest, a history of sexual abuse (Talley et al, 1997), certain cognitive attitudes and beliefs that can become dysfunctional (van Dulmen et al, 1996) and a peculiar confirmatory bias for negative material (Gomborone et al, 1993) are among the factors that are distinctive of IBS/FD and in certain circumstances may also act as risk factors for repeated consultations. Several factors may be specific for IBS/FD e.g. psychological morbidity, somatization and a greater responsiveness to seasonal changes while others e.g. early abuse and dysfunctional attitudes and beliefs, may represent risk factors for overuse of the health system.

The factors that are most influential of the decision to consult (that is, those that are significantly more severe in patients than in non-patients) are more directly associated with the severity of the disorder. Those who consult have more severe dyspepsia symptoms (Lydeard & Jones, 1989), more overall severity

of symptoms (Heitkemper et al, 1995), very real differences in all IBS symptoms (Heaton et al, 1991), more pain (e.g. Drossman, 1988; Heaton et al, 1991; Kettell et al,1992) and more disruption of bowel function (e.g. Heaton, et al, 1991; Heitkemper et al, 1995; Kettell et al, 1992). Compared with first time attenders, chronic attenders frequently have more constant symptoms, more chronicity and more social consequences (Guthrie et al, 1992).

The role of a mature coping style and an intimate confiding relationship as potential moderators of stressful transactions between the person and situations is in its infancy. Of the few studies available, one reveals an absence or an inadequacy of these potential 'buffers' in some patients with FD; another reports that patients with FD have more coping difficulties than patients with peptic ulcer disease, and another that past coping behaviours does not predict FGID symptoms long-term. These findings are presently inconclusive with regard to their moderating effects on the impact of stressful events.

Given the high degree of heterogeneity with respect to personality traits and coping style within IBS/FD samples, it is unlikely that a typical personality will emerge in the future. This does not deny the potential for certain personality traits to effect symptom intensity and IBS/FD function over time, for some individuals. In highly stressful circumstances, people with these traits are at greater risk of more frequent and more prolonged stress responses.

### **1.3 LIFE STRESS IN THE ETIOLOGY OF IBS/FD**

Although life event stress has been considered a core element in the pathogenesis of IBS since its initial description by Bockus and colleagues in 1929, empirical research is not always consistent with this. Consistent support, the following overview of the life stress literature suggests, is closely linked to the adequacy of the methodologies used. Thus, anecdotal, naturalistic studies, and formal assessments using comprehensive interview-based methods, are highly consistent in their reports of a strong association between the onset or exacerbation of IBS/FD disorders and recent exposure to particularly severe life stressors. In contrast, formal assessments of life events and daily hassles using questionnaire methods yield highly inconsistent findings. Several issues are relevant to a potentially causal relationship and these are assessed more effectively in some studies more than in others. They include the strength and consistency of the association, the temporal relation between life stress and the onset of symptoms, the exclusion of confounding influences, and the exclusion of reverse effects. Formal cross-sectional and longitudinal studies from 1960 to 1998 using interview or questionnaire methods to determine the role of life stress in IBS/FD are summarised in Appendices E and F respectively.

#### **1.3.1 ANECDOTAL EVIDENCE**

The literature is rich with anecdotal evidence linking life stress to alterations in gut function. Most people with IBS recall an episode of stress that preceded the onset of their symptoms (Chaudhary & Truelove, 1962) including the onset of their first bowel symptoms (Hislop, 1971), and most also report their

symptoms to be exacerbated by stress (Waller & Misciewicz, 1969; Whitehead, 1994). Patients with dyspepsia are more likely than orthopaedic patients to report that life events had aggravated or provoked their symptoms (prior to onset) and/or that they lived under high time and performance pressure (Jorgensen et al, 1986). As well as recent stressors, an emotionally disturbed childhood has been long associated with IBS. Stressors include early parental loss due to death or separation during childhood (e.g. Hislop, 1971; Macdonald & Bouchier, 1980; Hill & Blendis, 1967; Lowman et al, 1987), but also sexual and physical abuse (Drossman et al, 1990b; Longstreth et al, 1993; Talley et al, 1994). Compared with the general population and other patient groups, a history of sexual abuse is associated with poorer health generally, more frequent health care utilization, and FGID in particular. The incidence and severity of GI symptoms (also psychological symptoms such as somatization disorder and major depression) are greater in women who have been abused than in those without a history of abuse (Gefland, 1996). While the exact nature of the relation between these early events and onset of IBS/FD (or functional abdominal pain) as an adult is unclear, personal observations of marked similarities between the language used in relation to early experiences and current stressors suggests an important connection; this possibility has not been addressed.

### 1.3.2 NATURALISTIC AND DISASTER EVIDENCE

Naturalistic studies, including studies of natural disasters, are consistent with anecdotal reports that functional GI disorders such as IBS/FD frequently develop within the context of highly stressful circumstances. All studies expand on the nature of the stressor experience that precedes IBS/FD and each shows that irrespective of the type of stressor experience the temporal relation is consistent

with causal propositions. Two studies suggest life stress to be of etiologic importance in FD, the first involves response to imprisonment (Stenback & Siurala, 1964) and the other to compulsory military service (Giacosa et al, 1987). Official records establish that 97% of the prisoners and 100% of the conscripts were dyspepsia-free prior to exposure. However, after some years of imprisonment, the prevalence of "epigastric distress" among the prison population was significantly higher than in a "factory subculture" control group (31% and 15% respectively). While the initial onset for many of the prisoners began after some years of confinement, development of dyspepsia occurred in almost half the young conscripts (49.4%) within two to five months of commencement of service. Anxiety was a prominent feature of the young recruits (aged 19 to 27 years) who developed dyspepsia symptoms, not eating habits, alcohol consumption, coffee or cigarettes. These studies suggest that the emotions aroused by compulsory confinement and compulsory compliance with military service requirements provoke dyspepsia symptoms in some individuals who were dyspepsia-free prior to exposure, the timing of exposure to onset increasing the possibility of a causal association.

Studies of natural disasters such as the popular uprising to overthrow a 25-year dictatorship in Romania in 1989 (Dumitrascu & Baban, 1991) and severe flash floods and mudslides in Puerto Rico in 1985 (Escobar et al, 1992) also report the onset or recurrence of functional bowel symptoms following intensely threatening experiences. The first involved the shooting of hundreds of people during street riot, the intense stress experienced by the whole community was associated with the onset of more new cases of IBS than for the same period during the previous year and an increase in painful episodes (but not diarrhoea) for those who already had IBS. Respondents in the second (prospective) study

had been interviewed twice using the Diagnostic Interview Schedule for somatic symptoms, once approximately a year before the flash floods and mudslides and again approximately a year after the disaster. Exposure (lived in an affected area, experienced losses, faced serious risk) compared with non-exposure was associated with a higher prevalence of medically unexplained physical symptoms, particularly GI symptoms (abdominal pain, vomiting, nausea, excessive gas), some pseudoneurological symptoms (amnesia, paralysis, fainting, unusual spells/double vision) but few cardiorespiratory symptoms.

### 1.3.3 FORMAL ASSESSMENTS

Two methods have been used with unequal success to determine the relation of life stress to the subsequent onset or exacerbation of IBS/FD. In this review of the life stress literature in IBS/FD, the least consistent findings are among studies using the self-report life stress questionnaires (life event and daily hassles scales); the most consistent findings are associated with the use of the comprehensive interview methods of Brown and Harris, The Life Events and Difficulties Schedule (LEDS) (1978). These differences are not peculiar to this literature alone. Paykel (1983) in his review of life stress methodologies details empirical evidence from multiple sources showing self-report checklists to be seriously deficient in two areas in particular - data collection, and failure to remove events actually caused by the illness. Data collection by questionnaire, Paykel points out, does not permit the collection of sufficient detail to differentiate a trivial occurrence from an event that crosses the threshold to warrant being scored as an event, while failure to exclude events which are the effects of (or are influenced by) the illness itself seriously confounds cause and effect. These innate problems are reflected in poor concordance between subject and informant

(usually a relative) as to the presence of an event. For example, agreement in one study ranged from 46% for hospitalisation of family member to 79% for arguments with spouse, but only 69% for birth or adoption of child (Horowitz et al, 1977)! In contrast, using the more comprehensive LEDS in their study of patients with depression, Brown and colleagues (1982) obtained a concordance of 78%, reaching 91% for severely threatening events. A distinction of considerable relevance to the initiation of changes in gut function in IBS/FD not mentioned by Paykel, is the duration of the stressor. Intuitively, chronic stressors are much more likely than transient events to contribute to such profound changes in function.

### **Cross-sectional evidence**

Twelve controlled studies (Appendix E) have used self-report inventories to measure life event stress; one also includes a hassles scale. Neither a positive or negative association can be concluded from these findings which are in conflict on every life stress parameter. There is no agreement among studies with respect to the mean total life events scores, the frequency of life events, life change (the sum of positive and negative events) and the magnitude of impact (severity by frequency) scores. On each parameter, the patient group of interest (IBS, FD, functional abdominal pain, chronic abdominal pain) has differed or not differed with remarkably equal frequency from both healthy and other patient (organic GI disease, organic gallstone or urinary calculi, appendix) groups. That is, neither positive and negative findings predominate. Further, even when relations are positive, they are by no means consistent with the strength suggested by anecdotal and clinical evidence (Whitehead, 1994). With respect to the frequency and the severity of hassles (such as losing or misplacing something, not having sufficient

time for family, and concerns about pollution) patients with FD and dyspepsia-free individuals do not differ. It is unclear what accounts for the differences between studies (and weak associations) if it is not the measure itself.

Conflicting, weak, and unexpected findings are also reported in relation to the effects of life stress on consultation behaviour. Lydeard and Jones (1989), comparing consulting and non-consulting dyspepsia patients in general practice, used an open ended interview method with reference to published schedules of life events (Holmes & Rahe, 1967) to assess recent life events. They found stressful life events to be more frequent in consulters than in non-consulters but not to differ in their impact. Also, although consulters have significantly greater symptoms severity than non-consulters, the frequency of life events does not correlate with the severity of dyspepsia symptoms, as one might expect. Moreover, after concerns about the seriousness of symptoms are taken into account, life events are insufficiently strong to contribute further to the decision to consult. In contrast to this expected trend, Drossman and colleagues (1988) found *IBS non-consulters* to have significantly higher frequency of stressful life events and higher impact scores than either IBS patients or control subjects whose scores were similar. This finding contradicts all previous trends. To conclude, the importance accorded to any of these findings is diminished by reliance on a life stress instrument that has proved to be unreliable (Paykel, 1983) and is insensitive to individual differences in social contexts and stressor-appraisal.

Credence in the area of life stress should be accorded to studies which have employed more comprehensive and sensitive measures of life stress in FGID, in particular the interview-based Life Events and Difficulties Schedule (LEDS) of Brown and Harris (1978). In all studies using this technique, severe threatening stressors and/or psychiatric disorders have preceded onset or

exacerbation of FGID, the association being stronger for functional than for organic GI diseases (Craig & Brown, 1984; Beurepaire et al, 1992). For example, Creed (1981) reports that severe events which predict for the individual lasting threat or unpleasantness (e.g. separation, pending divorce) are more prominent in the etiology of the non inflamed appendix than in acute appendicitis. Events predicting long-term threat and chronic difficulties also precede onset of depression (Brown & Harris, 1979), which frequently coexists with IBS/FD. The first study to involve a mixed group of patients with functional GI disorders (including 45% with IBS/FD), also report that severe threatening (long-term) events and major (chronic) difficulties are more strongly associated with the onset/exacerbation of FGID than of organic GI disorders (Craig and Brown, 1984). Creed and co-researchers(1988) support this finding also in patients with various FGID (Appendix E). The relevance of these findings to specific FGID of interest, IBS and FD, and the relative contribution of acute events and chronic stressors had not been addressed. A case-control study by the present research team found life stress to be strongly associated with the onset or exacerbation of a particular disorder, functional (non-ulcer) dyspepsia (Bennett et al, 1991). Moreover, although a broad range of psychological variables were positively associated with FD, by far the most important was a stressor that was severe, threatening and prolonged (on average persisting for 12 months or more). A "highly threatening chronic difficulty" was experienced by almost all FD patients (98%) prior to onset/exacerbation of symptoms, but was rare in the community sample (2%) (Bennett et al, 1991). While the 'etiologic' timing of the life stressor assessments for the patient groups (i.e. prior to onset/exacerbation of FD symptoms) is an important feature of all of these studies the latter study identified chronic highly threatening stressors as the stressor most likely to provoke or

exacerbate FD symptoms. The long period of stress prior to the full development of a diagnosable disorder of gut function discounts the proposition that psychological disturbance is simply the consequence of the pain and discomfort of the gut disturbance or that it provokes consultation.

Acute events, depending on their severity, are more likely than chronic stressors to fulfil multiple functions in these disorders. Short-term events alone are not expected to play an important role in the development of IBS/FD given that their discrete and transient impact allows rapid physiological recovery. In support of this, people with FD do not experience a greater number of antecedent acute life events than people without dyspepsia - however, they do experience more events with long-term implications of severe threat within the etiologic period (Creed et al, 1988; Bennett et al, 1991). The marked clustering of these events during this period and the strength of their association with FD after excluding the effects of chronic stressors (Bennett et al, 1991), suggests that these events cannot be discounted as unimportant. Their effects may be more nondescript than the proposed causal effects of the severe chronic stressor. It is possible that in the presence of long-standing stress, severe events may act to trigger symptoms and/or the person's subjective appraisal of their severity or significance. It may also increase the likelihood of professional consultation.

In summary, two methods have been used with unequal success to retrospectively explore the relation of life stress to the subsequent onset or exacerbation of IBS/FD - life event checklists and the LEDS procedure. Using the more sophisticated techniques of the latter, the stressor most likely to provoke these disorders has been identified as severe and highly threatening. One study also suggests that at least one of the stressors associated with the development of

these disorders is likely to be chronic. The following examines prospective evidence.

### **Longitudinal evidence**

Using an open-ended interview technique two research groups documented the progress of patients with IBS-like symptoms over several years (Chaudhary & Truelove, 1962; Waller & Misiewicz; 1969) (Appendix F). At each contact, bowel symptoms, psychological status, life stress and the disruptive effects of symptoms on life style were monitored in detail - in particular, improvements and relapses in symptoms and life stress over time were recorded. Neither study used standardised measures. Chaudhary and Truelove found that life stress influenced the onset and course of bowel symptoms in four out of every five of their subjects, in women more than men (86% vs 65%). Observations by Waller & Misiewicz (1969) that stressful situations were etiologic to IBS, but not to ulcerative colitis, were supported several years later by Mendeloff et al (1970) who formally compared these patient groups. Chronic stressors, and stressors with the potential for long-term distress predominated (e.g. marital difficulties, problems with children, care of elderly parents etc.) suggesting that the interview technique broadly tapped life stress situations, and incidentally includes chronic as well as acute stressors.

Once again, the interview proves to be the more sensitive technique to assess etiologic life stress in IBS/FD. That is, of the five remaining longitudinal studies, three report no causal effects for life events in essential dyspepsia (Talley & Piper, 1986a), and for daily hassles in IBS (Suls et al, 1994; Dancey et al, 1995). Only two studies found that symptom severity altered as a function of life stress; the effect in both studies are small. Whitehead et al, (1992) reports that

three monthly responses on the Life Events Schedule over a 12 month period explains only 11% of the variance in bowel symptoms in patients with IBS. A similar statistic is not available in the second study (Dancey et al, 1998) although we know from their model of best fit that after allowing for symptoms and hassles during the previous two days, hassles on the same day have a small but significant additional effects on current symptom severity. As these observations are a day apart only, it could be argued that this model is more concurrent than truly prospective and, as such, does little to reduce the confounding of cause and effect that is inherent in cross-sectional correlations. Stronger causal inferences might have been drawn if the variable, daily hassles during the previous two days, had been significant after controlling for symptom severity prior to the previous two days thereby adjusting for powerful autocorrelation effects whereby an observation will correlate with its earlier observation. Suls (1994) who did control for the stronger effects of previous symptoms, conclude that prior and concurrent daily hassle stress have no consistent effects on subsequent symptoms.

Overall, in contrast to observational data, these prospective studies infer, at most, a minor effect by life event stress. In reference to this, Whitehead (1994) comments that “much harm could be done by prematurely rejecting the stress hypothesis for irritable bowel syndrome or other psychophysiological disorders because this hypothesis is so deeply entrenched: It is widely believed by clinicians, patients, and the general public; it is supported by many clinical data; and it is the theoretical basis for effective treatment” (p101). He also suggests that the conclusions drawn by Suls (1994) and his own team (1992) “that stress contributes minimally to irritable bowel syndrome, need to be tempered in the light of these observations” (p102). In fact, longitudinal studies testing the

relation of life events and daily hassle stress to IBS have failed to match expectations of a strong association.

### **Methodological issues - a better approach?**

Investigators have variously conceptualised, and variously explored, the relation of chronic life stress to subsequent symptom severity in patients with chronic IBS; their different approaches are most clearly reflected in the methods and measures they have used. Methodological issues that do not receive adequate attention using life event and daily hassle measures include:

1. the problem of *independence of life stress* from,
  - a) IBS symptoms (the issue of confounding cause and effect) and
  - b) psychological factors (the issue of confounding life stress with personality or emotional distress)
2. the *reliability of the severity of life stress ratings* (the issue of attaining accurate and objective severity assessments).
3. the selection of *an appropriate time-scale and overall methodology* (the issue of matching the methodology to the nature and course of the disorder which is relevant also to the concept of provoking profound alterations in the performance of normal [adaptable] gut functions).

The only measure designed to adequately deal with the problems of independence and reliability is the Life Events and Difficulties Schedule (LEDS) of Brown & Harris (1978). In our own work, the choice has always been to include only those stressors that are rated as fully independent of IBS symptoms and their disruptive effects on life-style. Independence of the predictor and outcome variable (stressor and symptoms) in this longitudinal study is seen as having particular relevance. For example, the relation between these variables can

be assessed after controlling for the effects of potential confounders such as personality and distress with confidence that these variables are as independent of the symptom outcome as can be achieved.

To reiterate with respect to reliability, inter-rater assessments and subject-informant (spouse) agreements are significantly higher in studies using the LEDS than in those using life event scales, especially for severe threatening events (Paykel, 1983). It is anticipated for this longitudinal study, that consecutive interviews using the LEDS will enhance the checks and balances inherent in this process and maintain (and perhaps improve) reliability.

The time-scales used for the study of daily hassles and life events differ considerably - ranging from daily assessments over three to five weeks for hassles, to two to three monthly assessments over twelve months for life events. Selection of a time-scale for chronic stressors in this study was based on the minimum duration of a chronic stressor, that is, six months. This selection was based on the expectation that the presence or absence of a stressor of this duration may be required to bring about major changes in symptoms severity over time. This framework is more realistic with respect to the statistical control of baseline symptomatology in order to determine the strength of the relation between stressor and subsequent symptoms *over and above* what might be expected from baseline symptomatology alone. For these and other reasons, it was the author's view that the LEDS was the most appropriate means of assessing the role of chronic stressors in IBS over time.

## 1.4 PSYCHOPHYSIOLOGY IN IBS/FD

Epidemiological evidence strongly supports a prominent role for psychosocial factors in IBS/FD. This section reviews the relation of psychosocial status to alterations in gut function (dysmotility, hypersensitivity) in these patients. The traditional approach has been to determine the effects of acute laboratory stress on gut motor activity in both healthy and IBS/FD participants. These effects are now better understood. For example, laboratory studies using tasks that are intellectually demanding and involve time pressure, have shown that stressors alter gut motility in healthy subjects; usually, but not always, motility is suppressed. Research relating psychological factors other than stress to sensory, motor or sensorimotor dysfunction in IBS/FD is scant. The following summarises what is known about the effects of laboratory stress and other psychological factors (eg distress, personality and coping) on sensory and motor function in the stomach, the small intestine, and the large intestine, in patients with these disorders. The major focus is research that is based on improved technology which has extended our understanding of normal and abnormal pathophysiology eg. early studies (Martin,1950; Roth et al, 1953; Weeks, 1946) relating laboratory stress to small bowel motility patterns were hindered by lack of knowledge of the normal cyclical variations in small bowel motor activity.

### 1.4.1 THE STOMACH

Psychological factors have long been implicated in the pathogenesis of FD (Truelove & Reynell, 1972; Hislop, 1977; Lagarde & Spiro, 1984; Thompson, 1984), and anecdotal and experimental evidence support various hypotheses

pertaining to disorders of secretion (Badgley et al, 1969), vascularity (Bergmann et al, 1991), motility (Wholf, 1943; Thompson et al, 1982; Camilleri et al, 1986b; Nyren, 1988; Talley & Phillips, 1988; Colin-Jones, 1988) and sensitivity in FD (Mearin et al, 1991). Laboratory studies consistently indicate that both acute (e.g. hand immersion in cold water) and sustained psychological stressors (e.g. prolonged dichotomous listening) produce transient alterations in upper gastrointestinal motor activity in healthy subjects (Thompson et al, 1983; Camilleri et al, 1984; Camilleri et al, 1986b; Kellow et al, 1992a). The changes observed are similar to the gastric antral hypomotility and delayed gastric emptying observed in a significant proportion (30 - 40%) of FD patients in the basal state (Camilleri et al, 1986b). Patients with gastric dysmotility, or suspected dysmotility, seem to respond to acute stress with a generalized suppression of gastric motor (Camilleri et al, 1986b) and autonomic (Jorgensen et al, 1986) activity. However for FD patients with reduced motility at baseline, antral dysmotility is not suppressed further (e.g. Hveem et al, 1998). While it is feasible that chronic distress associated with life strain (Jorgensen et al, 1986) or exposure to a chronic life stressor (Bennett et al, 1991; Giocosa et al, 1987; Stenback & Siurala, 1964) may link acute responses and intermittent gastric motor dysfunction with more sustained gastric motor dysfunction, this remains to be demonstrated.

As there is little research linking specific psychological factors with measures of gut function, the psychophysiological mechanisms involved are poorly understood (Camilleri et al, 1986b). One study reports indices of personality derived from the MMPI and psychiatric evaluation to be unrelated to gastric motor dysfunction in FD (Camilleri et al, 1986b). Various other factors which have been implicated in the aetiology of functional gut disorders remain to be studied in relation to gastric motor dysfunction. These include specific personality traits (e.g.

neuroticism, trait anxiety, aggression and irritability), maladaptive methods of coping with stress, anxious or dysthymic states, somatic anxiety, social dependence and affect expression (Bennett et al, 1991; Kellow & Langeluddecke, 1989; Clouse, 1988; Uvnas-Moberg et al, 1991).

#### 1.4.2 THE SMALL INTESTINE

Although for patients with IBS, the colon has attracted most attention in the past, it now appears after a relatively short period of investigation that the small intestine is at least as likely to be a site of abnormal motor and/or sensory disturbance in individuals with this disorder. Also, even though available data are still limited, the small bowel appears to generate patterns that are closely associated with the development of symptoms (McKee & Quigley, 1993b).

For most patients with IBS, motility patterns of the small bowel are disturbed, that is, disrupted, absent or aberrant. Disturbances can be meal related or occur in the fasting (interdigestive) state. *Meal related (postprandial) motility* follows a distinct pattern that accomplishes three functions - mixing the food with digestive secretions, circulation of chyme so that mucosal contact is maximal, and propulsion of contents in a net aboral direction. Activity between meals follows a cyclical motor pattern known as the *migrating motor complex (MMC)* which consists of three main phases - phase 1 (motor quiescence), phase 2 (a period of random and irregular contractile activity that propagates over short distances), and phase 3, or the activity front (a sequence of uninterrupted, high amplitude, rhythmic contractions of several minutes duration which migrate over long distances). The MMC is the major determinant of transit and clearance of food debris and secretions in the small bowel. No distinctive pattern resembling the MMC has been identified in the colon. The motor events responsible for transit,

as opposed to mixing, are not well understood although transit is fastest when localised propulsive events are closely coordinated so that they propagate distally.

A number of abnormalities in fasting motor activity have been described in patients with IBS including alterations in the periodicity of interdigestive cycles, some of which appear to be associated with IBS symptomatology (more frequent migrating motor complexes in those with IBS and diarrhea, less frequent MMCs in those with IBS and constipation) (Kellow et al, 1990; Kellow & Phillips, 1987). Of particular significance is the finding of an increased prevalence of phase 2 clustered contractions in the duodenum and jejunum of IBS patients; this motility pattern is seen only during waking (Kumar & Wingate, 1985; Kellow et al, 1990), is independent of whether diarrhea or constipation symptoms are predominant (Kellow et al, 1990; Valori et al, 1986) and is associated with abdominal pain in some IBS patients with this motility pattern (Kellow & Phillips, 1987). In the ileum (the distal small bowel), pain has been reported in association with the occurrence of giant phase 3 contractions. Although this pattern may occur in healthy subjects, it is painful only in patients with IBS (Kellow et al, 1990). A hyper-reactive motor response to balloon distension in the terminal ileum is another aspect of small bowel motility that differentiates IBS patients from healthy subjects (Kellow et al, 1990). A similar pattern of hyper-reactivity in the colon has been described in patients with IBS (Fukudo, Nomura, Muranaka & Taguchi, 1993). The relevance to IBS symptomatology of more subtle variants in phase 2 and phase 3 motor activity is presently unclear (Kellow & Bennett, 1996).

An interesting aspect of the effects of psychological stress on small bowel motility is that acute and chronic experimental stressors seem to have very different effects. Transient changes elicited by acute psychological stressors in

the laboratory situation do not differ in most cases between IBS patients and healthy controls (Kellow et al, 1992a). In contrast, a long period of intermittent psychological stress inhibits the occurrence of MMCs during waking (Kumar & Wingate, 1985; Valori et al, 1986), increases the duration of phase 2 motor activity, and shortens the phase 1 quiescent period (Fukado et al, 1993). Motor recordings of small bowel motility in the postprandial state suggest that jejunal motor responses are generally intact - that is, although some may have a shorter duration of the fed pattern and a high amplitude and frequency of contractions, no major abnormalities have been observed (Kellow et al, 1990; Kellow et al, 1988). The effects of psychological stressors on ileal motility have not been studied.

*Small bowel transit* also is influenced by experimental stressors. Cann and colleagues found that although a difficult 4-hour dichotic listening task significantly speeded mouth to caecum transit in all healthy subjects (Cann et al, 1983a) in patients with IBS it was variable, that is, transit was significantly increased in diarrhea-predominant IBS and significantly slowed in constipation-predominant IBS (Cann et al, 1983b). Despite the limitations of the methodologies used (lactulose-breath hydrogen test and oro-caecal, (not small intestine) transit), these findings have been supported in studies using other methodologies (Jian et al, 1982; Jian et al, 1984; Nielsen et al, 1986).

*Balloon distension* is another type of gut stimuli that may be applied in the laboratory situation; it has been used to assess levels of conscious perception of mechanical events throughout the gut in health and IBS. In the small intestine, the threshold for perception of stimuli is lower than normal for most patients with IBS. An early study demonstrated a low threshold for discomfort in response to balloon distension in the ileum (Kellow et al, 1988); this has been confirmed in several other regions of the gut. An enhanced perception of the passage of the

activity front (phase 3 of the MMC) in the duodenum has also been documented in patients with IBS (Kellow et al, 1991); the amplitude of the activity fronts that are perceived, being greater than those not perceived. The jejunum is also hypersensitive to mechanical (but not electrical) stimuli; importantly, sensitivity is not due to reduced gut compliance in patients with IBS (Accarino et al, 1995). Jejunal sensitivity can be modified by complex interactions arising from different stimuli in different regions of the gut, such as entry of nutrients into the small intestine or distension of the rectum (Kellow & Evans, 1998). IBS patients also perceive provocative stimuli (nutrients, balloon distension; transmucosal electrical nerve stimulation) over a more diffuse area of the abdomen than healthy control subjects (Szurszewski,1981), suggesting a distorted referral pattern of gut sensation in these disorders (Azpiroz, 1995a).

Gut stimuli activate a variety of mechanosensitive afferent pathways, and in certain circumstances may induce conscious perception; this is currently an area of active research. It has been noted, for example, that somatic stimuli (transcutaneous electrical nerve stimulation applied on the hand) decrease sensitivity to gut stimuli (probably through supraspinal mechanisms) while activation of the sympathetic nervous system by a process that does not involve any stress or cognitive processes (by lower body negative pressure), heightens visceral, but not somatic sensitivity (Azpiroz, 1995b). Furthermore, IBS patients appear to have an increased tolerance of somatic pain (Cook et al, 1987; Whitehead et al, 1990; Accarino et al, 1995). While decreased tolerance of visceral stimulation and increased tolerance of somatic stimulation may reflect a perceptual response bias, it also suggests that hypersensitivity in the small bowel is related to a selective alteration of intestinal mechanosensitive pathways (Accarino et al, 1995).

Present knowledge concerning interrelations between disturbances of motor activity, transit and sensitivity is incomplete. Also, as small bowel studies in patients with FD have received less attention than in patients with IBS, it remains controversial whether dyspeptic patients exhibit normal or enhanced sensitivity of the jejunum, despite a high prevalence of gastric hypersensitivity.

Although small bowel motility, sensitivity, and transit have all been shown to respond sensitively and selectively to psychological distress (Kellow & Bennett, 1996), and cognitive appraisal of a stressor (as threatening or harmful) appears to be the primary determinant of the magnitude of both the emotional and the gut response, it is somewhat surprising that the relation of psychosocial disturbance to small bowel dysfunction in these disorders is virtually unknown.

#### 1.4.3 THE COLON

##### **Motor activity**

In contrast to the MMC of the small intestine, colonic motor activity exhibits very little pattern. The typical response of the colon to noxious stimuli is increased motility. In comparison with healthy controls, the colonic motor response is more exaggerated in patients with IBS and can be elicited by any stimuli, including eating - in the large intestine this is manifest as an exaggerated gastrocolonic response. This reflex is common, characteristic of IBS and is accompanied by urgency of defecation and abdominal pain or diarrhoea in patients with IBS after eating (eg Sullivan et al, 1978; Wright et al, 1980). In addition to the hyper-reactive response, a marked decrease has been observed in the frequency and/or amplitude of motor contractions in the pelvic colon following provocation (Connell, 1962); the reduced peristaltic action of these

contractions could retard the movement of food and gas towards the rectum and anus and contribute to an altered bowel habit and pain in some IBS patients. Chaudhary & Truelove (1961) were the first to suggest that the basal colonic motility index is increased only while the patient with IBS is symptomatic and that during asymptomatic periods basal motility is normal.

The hyper-reactivity of the colon in response to stimuli such as physical or psychological stressors, balloon distension, and injection of peptides and the presence of non-peristaltic contractions, has a long history. The early classic studies of Almy and co-workers (Almy & Tulin, 1947; Almy et al, 1949b; Almy, 1951) remain among the best examples of the potential of experimental stressors to induce motor changes in the gut and the effects they documented have been replicated consistently. In demonstrating that colonic motility and mucosal blood flow increase in response to pain and powerful emotions such as fear, anxiety and anger, highly provocative painful stimuli were used e.g. cold pain and severe headaches (induced by means of a metal head clamp), and fear (induced by leading subjects to believe they have colon cancer). The exaggerated motor response to stress noted by Almy and colleagues (i.e. greater in IBS patients than in healthy subjects) has been replicated by many contemporary research groups, including Welgan and associates (Welgan et al, 1985; Welgan et al, 1988) and Fukudo and colleagues (Fukudo et al, 1993; Fukudo & Suzuki, 1987). In contrast to the enhancing effects on colonic or small intestine motility of powerful (and often prolonged) emotional states such as overt anxiety (Devroede et al, 1989b), vigilance (Schang et al, 1988), and anger, rage, or aggression, either overtly expressed or contained as resentment (Welgan et al 1985; Roth et al, 1953; Sadler & Orten, 1968; Whorwell et al, 1992), mild to moderate inhibition of motility is associated with emotional states such as depression (Almy et al 1949b; Chaudhary

& Truelove, 1961), sadness, natural sleep, contentment, withdrawal (Sadler & Orten, 1968), hypnosis and happiness (Whorwell et al, 1992) and deep relaxation (Kellow et al, 1992b). Only abject fear or paralysing horror have been associated with cessation of gut motility (Cannon, 1902; Sadler & Orten, 1968). In the sigmoid colon, active relaxation also has a much smaller influence on sensations of pain and gas than psychosensory stimulation such as an anxiety-provoking dichotomous listening task during progressive balloon distension (Ford et al, 1995).

From the paucity of evidence available, there is no suggestion that psychopathology, as assessed by psychometric methods, has any effect on colonic motor activity. The first study to address this issue (Whitehead et al, 1980) found no relation on any colonic motility parameter with any of the nine subscales of the Hopkins symptom checklist or their combinations. Welgan et al (1985) and Fukudo et al (1993) found no association using the MMPI.

### **Transit**

Very little information is available also on the effects of psychological factors, other than experimental stress, on colonic transit in patients with IBS. In psychiatric patients, a comparison with healthy individuals reveals that intestinal transit times (ITT) are significantly faster in patients with predominant anxiety, and significantly slower in patients with predominant depression, but ITT does not correlate with levels of psychometrically assessed anxiety or depression (Chaudhary, 1989). These findings have been replicated in part by a similar study (Gorard et al, 1996) which supports a faster (whole gut) rate of transit in patients with anxiety disorders and no relation with transit for patients with depression. Gorard's study is the first to suggest that psychometrically assessed levels of

depression (but not anxiety) correlate negatively with whole gut transit time. These findings are generally consistent with earlier reports that prolonged anxious and depressed states have different effects on colonic motility. In particular, the effects of anxiety, overall psychological distress, and experimental stressors, on lower gut transit are very similar; mostly (but not always) they speed colonic transit. Thus, in outpatients with severe idiopathic constipation a measure of overall psychological distress (the general severity index of the SCL-90-R) negatively correlates with total colonic transit times suggesting that the greater the level of distress, the faster the speed of transit is likely to be (Grotz et al, 1994). This is consistent with the hyper-reactive effects of experimental stressors on colonic transit/gut motility and with Chaudhary's findings of faster transit in psychiatric patients with predominant anxiety. However, in patients with idiopathic constipation and slow transit, free-floating anxiety correlates positively with rate of transit in the ascending colon i.e. the higher the anxiety score, the slower the transit in this group of patients (Devroede et al, 1989b). While this is not dissimilar to gastric hypomotility in some patients with IBS, and slow transit in the small intestine of patients with constipation-predominant IBS in the rested/basal state (Cann et al, 1983b), the vast majority of studies of the colon suggest that stress profoundly increases colonic motor activity, at least in the short term. In a recent study of women with IBS, Dumitescu and Granescu (1996), using the life events scale of Holmes and Rahe (1967), found no correlation between life stress and prolonged colonic transit. At present, apart from anxiety, general distress, and to a lesser extent depression, there appear to be no consistent psychosocial correlates of colonic transit in FGID.

## Sensitivity

Ritchie (1973) was the first research group to show that IBS patients report pain at lower volumes of balloon distension in the sigmoid colon. A recent resurgence of interest in visceral sensitivity has led to multiple replications of Ritchie's findings (eg. Whitehead et al, 1990) and a considerable extension of their work. Subsequent studies have shown that sequential inflations throughout the gut can trigger sensations (e.g. gas, urgency to defecate) as well as pain, of the same quality and in the same site as the presenting symptoms (Swarbrick et al, 1980). Others have shown that increased sensitivity to balloon distension is not confined to the colon in patients with IBS; increased sensitivity has been demonstrated in the esophagus (Constantini et al, 1993), the stomach (Zigheboim et al, 1995) and the small intestine (Kellow et al, 1988; Evans et al, 1996). Importantly, increased sensitivity does not reflect a generalized hypersensitivity to pain and discomfort. The low threshold to perceive gut sensations, that are generally blocked from consciousness, appears to be specific to pain and sensations in the GI tract. Research has shown IBS patients to have normal thresholds for somatic pain induced by ice water immersion (Whitehead et al, 1990), and to have *increased* thresholds for touch and for painful electrical stimulation of the nondominant hand (Cook et al, 1987). It is generally agreed that the presence of sensitivity of the rectosigmoid colon in IBS patients who experience spontaneous symptoms of chronic abdominal pain/discomfort, may be taken as evidence for chronic visceral hyperalgesia (Mayer et al, 1995). However, until the nature of heightened visceral sensitivity has been characterised - in particular, its sensory and affective parts (Mayer et al, 1995), controversy is likely to continue as to whether altered rectal perception represents a biological marker for IBS as suggested by Mertz and colleagues, (1995).

The mechanism of the visceral hypersensitivity of patients with IBS is not fully understood. Although peripheral sites (that encode altered sensory function and are themselves effected by multiple local and peripheral influences) and central processing mechanisms converge to determine the final conscious perception, the cortex exerts final control of visceral perception. Thus, irrespective of peripheral encoding mechanisms, conscious perception is critically dependent on the central nervous system's integration of afferent inflow. In a series of very carefully designed studies, Azpiroz and his team (e.g. Accarino et al, 1993) have shown that attending to the stimulus increases perception of intestinal distension, as compared to mental distraction or relaxation. Another study notes that compared with healthy controls, a different part of the brain is activated by rectal stimulation in patients with IBS - the lateral prefrontal cortex instead of the anterior cingulate gyrus (Silverman et al, 1997). From yet another perspective, Ford and colleagues (Ford et al, 1995) tested the effects of mental stress and relaxation on the sensation of gas and pain in the colon in healthy volunteers. Their findings strongly support their hypothesis that psychosensory stimulation increases the perception of stimuli in different regions of the colon; mental stress significantly increasing anxiety and the sensation of gas and pain during distensions in the sigmoid colon. Active relaxation exerted a smaller effect on sensations in the colon - it had no effect on pain, but reduced the sensation of gas. It seems that psychosensory stimulation and baseline conditions (initial colonic sensory scores, pain sensitivity) have powerful short-term effects on colonic sensation.

The effects of psychological processes on sensation thresholds has also attracted research interest. Most (but not all) psychometric data suggest that the lower threshold for visceral pain found in IBS patients is not related to measures

of 'psychoneuroticism' (e.g. anxiety, depression, neuroticism,) (Latimer et al, 1979a; Whitehead et al, 1990). Among women with and without IBS, and without a history of sexual abuse, Whitehead and colleagues (1997) report that the severity of anxiety (according to a subscale of the Trauma Symptom Checklist) and of somatization of affect (according to 51 psychological symptoms of the Cornell Medical Index) correlate with *moderate* thresholds for reporting rectal pain (Whitehead et al, 1997). While these findings suggest that high levels of anxiety may sensitize the rectum over time, additional analyses discount the notion that this relationship is influenced by a history of sexual abuse or that it is specific to IBS. With respect to perception of nonpainful sensations during progressive balloon distension, Prior and co-workers (1993) found that high levels of anxiety (a score of more than 10 on the Hamilton Anxiety and Depression scale), but not depression, are twice as common in patients with IBS with enhanced rectal sensitivity, most of whom also had anorectal hyper-reactivity (Prior et al, 1993). That is, enhanced rectal sensitivity identifies a subgroup of IBS who are anxious, have an increased desire to defecate, increased rectal compliance and a reduced threshold for rectal motor activity. No study it seems has tested the relation of psychosocial factors to perception sensitivity (defined in this work (Study 5) as the first perception of the presence of the balloon).

#### 1.4.4 SUMMARY

It is relevant to the etiopathogenic mechanisms of IBS that the transient sensory and/or motor disturbances which can be provoked in healthy subjects by acute psychological stressors, are similar to the dysmotilities and the

hypersensitivities observed in a significant proportion of IBS patients in a non-stressed state.

The effects of acute stress on gut motor and sensory function are now better understood. During stress, gastric motility is inhibited and gastric emptying delayed and prolonged; in the small intestine, some types of stressors can increase the frequency of the cyclical bursts of contractions during fasting, and have a variable effect on small bowel transit. In the colon, contractile activity increases during stress.

Experimental stressors clearly have the potential to mimic the interaction of psyche and gut function, also, central effects on visceral motor and sensory function are powerful even if the mechanism is poorly understood. It is agreed that conscious perception of normal as well as abnormal visceral information is clearly compromised in IBS. One possibility suggested by Mayer (1996b) is that the mechanisms that usually inhibit conscious perception of these stimuli are compromised allowing hypersensitivity to develop. While at present there is no hard evidence to strongly support the concept that chronic traumatic experiences may be involved, the concept of neuroplastic changes of central structures due to early traumatic experiences (eg. sexual abuse) has received at least theoretical support. In part, this explanation suggests that memories of these events and their emotional impact are stored in memory banks within the limbic system and recalled when related to current circumstances, or alternatively, chronic stress of a highly threatening nature may be linked in a nonspecific way to the general stress response (Mayer, 1996b).

Although it is unclear whether frequent and prolonged stress reactions (such as those provoked by chronic real-life stressors) slowly modify normal patterns of contractile activity or whether they sensitize gut reactivity over time,

the possibility is supported by several lines of research. We have seen that in the laboratory and in a real-life situation, psychosensory stimulation has been shown to have powerful effects on sensory and/or motor dysfunction. In the laboratory situation, psychological distress (approximating anxiety) and colonic sensory sensitivity is induced in healthy volunteers. In the case of the onset of IBS following infectious diarrhoea, anxiety (psychometrically assessed) is the primary determinant. While in both situations either the psychological or the physical stimulus may provoke alterations in sensory and/or motor function, the effects are more certain when both are present, particularly in the onset of IBS following infectious diarrhoea.

Few experimental studies gather or report information concerning the affective component of the stress response whether the stressor is physical or psychological. Apart from one study which provoked a specific emotion, anger, via the medium of hypnosis, usually it is assumed that each subject's affective response to an intellectually demanding and prolonged mental stressor (eg. dichotomous listening) is the same, anxiety. No record is kept of how often elements of anger, frustration, resentment, self-reproach or reduced self-efficacy are experienced, how often these emotions are suppressed or overtly expressed or whether they influence the type of gut response, its severity or its duration. Rao's recent comparison of the effects on the human colon of physical and psychological stressors illustrates clearly that the colonic motor responses to these stressors differ - they differ in type of response, duration of response, the presence/absence of a concomitant autonomic response and the recovery period (Rao et al, 1998). Both stressors enhance colonic motor activity but psychological stress induces a prolonged response with propagated activity and without appreciable autonomic response. The physical stressor (cold stress)

induces more simultaneous contractions with increased pulse rate and blood pressure. During recovery however, motor activity returns to baseline after physical stress, but remains high after psychological stress. Although it is assumed that these differences are due to differences in the type of stressor; it is equally possible that the somatic responses reflect differences in the unknown affective component of the stress response.

Another approach is to relate a broad range of psychosocial factors to the severity and extent of altered transit in various regions of the GI tract and to motor, sensory and sensorimotor function within patients with FGID (IBS and FD in particular). The aim is to identify patterns of psychophysiological dysfunction within these disorders. From the above review it is clear that very few researchers have adopted this approach, hence it is argued (eg. Valori, 1998) that psychosocial factors should be included not only for completeness, but because it is possible that visceral dysmotility and hypersensitivity are intermediate events between psychological distress and symptoms. Much of our own work (studies 3, 4 and 5 of the present thesis) is based on this premise.

In summary, despite rapid progress in understanding and identifying specific abnormalities within the two-way communications of the psyche and bowel over the last few years, progress is slow with respect to showing that real-life chronic stress has more than a small effect on sensorimotor function in IBS, or that some apparently conflicting findings may be explained, at least in part, by psychophysiological differences within these disorders.

## 1.5 RESEARCH AIMS AND HYPOTHESES

The main objective of the following series of studies is to examine *the relation of psychosocial factors - life stress, psychological distress and personality - to the number and type of FGID, to the course of symptom intensity in IBS over time, and to gastrointestinal motility, sensitivity and transit in FGID.*

The following specific aims are related to either symptom-based outcomes (studies 1 and 2) or gastrointestinal motility outcomes (studies 3, 4 and 5).

### 1.5.1 AIMS

#### **Symptom-related outcomes**

##### STUDY 1: CROSS-SECTIONAL EVALUATION OF PSYCHOLOGICAL, SOCIAL AND EXTRAINTESTINAL FEATURES OF FGID

Based on the new diagnostic criteria for FGID and FGID subgroups, specific aims in terms of symptom-related outcomes are:

*Aim 1.* To determine in a large group of patients with various FGID (functional gastroduodenal and functional bowel disorders), the relative importance of specific psychological, social, emotional and extraintestinal (somatic) factors:

- a) to the severity and extent of functional gut disturbance (ie the *number* of FGID present) and/or
- b) to specific FGID (ie *type* of FGID).

*Aim 2.* To determine whether severe and chronic life stress threat predicts the nature and severity of concurrent gastrointestinal, extraintestinal and emotional symptomatology.

## STUDY 2: LONGITUDINAL EVALUATION OF LIFE STRESS IN IBS

The cross-sectional findings of Study 1 are extended by this longitudinal investigation to determine the relation of chronic life stress to subsequent symptom intensity over a follow-up period of 16 months in patients with IBS. The primary objective is to determine the extent to which the intensity of chronic life stress threat and/or goal-frustration influence subsequent levels of symptom intensity over time. More specific aims are:

*Aim 3.* to examine group and individual patterns of change in symptom intensity and life stress over time

*Aim 4.* to determine the magnitude of the effects within-subjects of life stress on subsequent symptom intensity over time, in particular:

- a) the *extent of covariance* of LS with subsequent symptom intensity over three assessment periods
- b) the *time-lagged relationship* of life stress to subsequent symptom intensity, over and above the effects of baseline symptomatology
- c) the contribution of *personality, coping style, emotional distress, age, and gender* on this relationship, and on subsequent symptom intensity
- d) the life stress predictors of *any improvement or lack of improvement in symptom intensity* over 16 months
- e) the life stress predictors of *clinical improvement* (ie a 50% improvement) or no clinical improvement over 16 months

*Aim 5.* to examine relations between depression, life stress and symptom intensity over time

- a) depression and symptom intensity
- b) life stress, depression and symptom intensity

## **Gastrointestinal Motility Outcomes**

New and more reliable scintigraphic, manometric and intraluminal distension techniques have been used to assess specific aspects of GI motility. The outcome variables in the following studies include delayed and normal transit outcomes - in the stomach (Study 3) and in the whole gut (stomach, small intestine and colon) (Study 4) - and motor (contractile) activity and sensitivity (perception) outcomes, in the jejunum of the small bowel (Study 5). Specific aims are:

### STUDY 3: EVALUATION OF GASTRIC EMPTYING IN FUNCTIONAL DYSPEPSIA

Aim 6. To determine in detail, in patients with functional (non-ulcer) dyspepsia (with and without IBS), the psychosocial features of gastric stasis (ie abnormal motor activity in one region only) on:

- a) four parameters of solid gastric emptying, and
- b) two parameters of liquid gastric emptying

### STUDY 4: EVALUATION OF WHOLE GUT TRANSIT IN FGID

Aim 7. To extend these findings using a wholly scintigraphic technique to assess gut transit in all three regions of the gut simultaneously to determine and compare among patients with FGID the psychosocial and demographic features of:

- a) delayed GI transit in one or more regions of the digestive tract, namely the stomach, the small intestine or the colon,
- b) widespread delayed transit (defined as delay in two or more regions), and
- c) normal transit in all three regions

## STUDY 5: EVALUATION OF JEJUNAL SENSORIMOTOR FUNCTION IN IBS

Aim 8. To determine in patients with IBS (with and without FD):

- a) the psychosocial features of hypersensitivity to distension of the small intestine, that is:
  - i. for initial (first) perception, and
  - ii. for pain threshold, and
- b) the psychological features of abnormal motor activity in the small bowel, in particular postprandial and fasting motor (contractile) activity in the jejunum, and
- c) the psychological differentiating features of patient subgroups, namely:
  - i. sensorimotor subgroup  
(the presence of heightened perceptual and pain sensitivity, abnormal postprandial and fasting motor activity)
  - ii. motor subgroup  
(normal sensitivity, abnormal postprandial and fasting motor activity),  
and
  - iii. fasting motor subgroup  
(normal sensitivity, normal postprandial motor activity and abnormal fasting motor activity)

### 1.5.2 HYPOTHESES

Overall these studies are based on the premise that (1) multiple psychological, social and physiological factors predispose to certain FGID, provoke and prolong FGID symptomatology and motor dysfunction, and largely determine the severity and extent of the disorder over time, and (2) that vulnerability to severe and extensive FGID (symptomatology, gut dysfunction)

increases over time according to the number, severity and duration of psychosocial risk factors in individuals predisposed to these disorders. For each study, this premise translates into specific hypotheses.

### **Symptom-related outcomes**

#### STUDY 1: CROSS-SECTIONAL EVALUATION OF PSYCHOLOGICAL, SOCIAL AND EXTRAINTESTINAL FEATURES OF FGID

Hypothesis 1. Psychological, social and extraintestinal (non-gut) disturbance will coexist in FGID such that:

- a) the overall severity and extent of functional gastrointestinal disturbance (the *number* of FGID present) will correspond with the intensity of psychological, social and extraintestinal disturbance, and
- b) psychosocial and extraintestinal disturbance will be a prominent feature of certain *types* of FGID.

Hypothesis 2. Chronic life stress threat will predict both the nature and the extent of concurrent multisystem (gastrointestinal, extraintestinal and emotional) symptomatology.

#### STUDY 2: LONGITUDINAL EVALUATION OF LIFE STRESS IN IBS

Hypothesis 3. In patients with irritable bowel syndrome, group and individual patterns of change in life stress and symptom intensity over time will be non-systematic (ie individually variable) with an overall trend to improvement over time.

Hypothesis 4. Life stress (specifically chronic and severe life stress threat) will have large and consistent effects on subsequent symptom intensity over time, in particular:

- a) life stress and symptom intensity will covary over three assessment periods ie incremental increases/decreases in symptom intensity will follow, and correspond with, incremental increases/decreases in life stress.
- b) the relationship will:
  - i. remain significant over and above the effects of baseline symptomatology and after a substantial (>6 month) time-lag,
  - ii. it will be quantitative, and
  - iii. the direction will be causally feasible ie life stress will predict symptom intensity, not the reverse.
- c) some personality, coping style, emotional distress, age and gender variables will also contribute independently to subsequent symptom intensity, however, only in the presence of severe and chronic life stress.

Hypothesis 5. Depression and symptom intensity will coexist, not because they are causally linked, but because each is independently provoked by antecedent life stress, specifically:

- a) depression will not predict subsequent symptom intensity, and symptom intensity will not predict subsequent depression, and
- b) life stress (ie one or more highly threatening chronic difficulty) will predict subsequent depression over and above the effects of baseline depression.

### **Gastrointestinal Motility Outcomes**

The following research hypotheses are based on the premise (1) that during periods of severe and prolonged stress, personal resources (eg psychological

and/or age and gender-related factors) may determine, at least in part, the presence, severity and extent of motor and/or sensory abnormalities within the digestive system of individuals with FGID (IBS and/or FD symptomatologies in particular), and (2) that gastrointestinal motor function alters in accordance with the on-going function of the *whole* individual. Thus, the psychological disturbance coexisting with gastric stasis (poor gastric tone/'suppressed' gastric motor activity) in Study 3, delay in transit in Study 4, and abnormal motor activity assessed by manometry in Study 5, will reflect a particular style of coping that employs cognitive-behavioural restraint to reduce stressful input and to control emotional reactions - for example, by avoiding stress-provoking persons and situations and by controlling and suppressing unwanted emotions such as anger. That is, the predominant mood state is most likely to be 'suppressed' and to reflect overt unhappiness. Based on this proposition, the tendency to be overtly angry, anxious and/or reactive is much more likely to be associated with a sensory disturbance, such as hypersensitivity to balloon distension of the gut (also assessed in Study 5), while the presence of abnormal motor activity as well as sensory disturbance (sensorimotor disturbance) would reflect a combination of the features of both motor and sensory disturbance. This global premise is the basis for the following hypotheses:

### STUDY 3: EVALUATION OF GASTRIC EMPTYING IN FUNCTIONAL DYSPEPSIA

Hypothesis 6. Among patients with FD (with and without IBS), the psychosocial features of solid and liquid emptying will be consistent with the restrained coping style referred to above across each of the following parameters of gastric stasis assessment:

- a) four parameters of solid emptying (solid  $T_{1/2}$ , solid delay, rate of emptying (RoE) at 45min and 70min), and
- b) two parameters of liquid emptying (liquid lag and RoE at 45min).

#### STUDY 4: EVALUATION OF WHOLE GUT TRANSIT IN FGID

Hypothesis 7. Among patients with FGID, delay in transit will be associated with a suppressed/depressed coping style and mood. Also,

- a) the psychosocial and demographic (age, gender) features of delay in transit in one region (DT1) and delay in transit in two or more regions (DT2) will differ quantitatively rather than qualitatively, and,
- b) these features will increasingly differentiate delay in transit from normal transit in all three regions (NT) as the number of regions of DT increase
- c) NT will have distinctive features.

#### STUDY 5: EVALUATION OF JEJUNAL SENSORIMOTOR FUNCTION IN IBS

Hypothesis 8. Among patients with IBS (with and without FD):

- a) the psychosocial features of *small bowel hypersensitivity* (ie hypersensitivity for initial perception and for pain threshold), and of abnormal postprandial motor activity in the small bowel will share common features (largely due to overlap among these abnormalities), however some qualitative and quantitative differences may be expected; also
- b) psychosocial features will differentiate between patient subgroups defined according to the presence of particular combinations of sensory and/or motor abnormalities.