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## **CHAPTER 2 METHODS**

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## 2.1 SUBJECTS

The patient sample comprised 350 outpatients with FGID gastrointestinal disorders (FGID), primarily irritable bowel syndrome (IBS) and one or more of the functional dyspepsia (FD) syndromes. Diagnoses were based on clinical evaluation of symptoms supported by normal findings at endoscopic, ultrasonographic, and other appropriate investigation. Differentiation into standardised subgroups according to the new classification system (Drossman et al, 1994) was determined from responses on a validated symptom questionnaire (Talley et al, 1989b). The study population represents the total of all participants in the following five studies:

STUDY	SAMPLE SIZE
STUDY 1: Cross-Sectional Evaluation of Psychological, Social and Extraintestinal Features of FGID	n = 188
STUDY 2: Longitudinal Evaluation of Life Stress in IBS	n = 117 <sup>a</sup>
STUDY 3: Evaluation of Gastric Emptying in Functional Dyspepsia	n = 28
STUDY 4: Evaluation of Whole Gut Transit in FGID	n = 110
STUDY 5: Evaluation of Jejunal Sensorimotor Function in IBS	n = 24

<sup>a</sup> Patients in Study 2 were a subgroup of participants in Study 1.

All patients underwent detailed semi-structured interviews and also completed self-report psychological and symptom questionnaires. Participants in Studies 3, 4 and 5 also underwent gastrointestinal motility function assessment. Psychosocial, symptom and motility data were collected in a blinded and independent manner.

#### 2.1.1 ELIGIBILITY CRITERIA

During the data collection period for each study, patients were recruited consecutively from particular patient populations if they satisfied specific eligibility criteria.

Standard eligibility criteria required of all participants:

1. A cluster of symptoms that satisfied the diagnostic criteria of one (or more) FGID subgroup, from three classes of FGID (see Appendices A & B), namely:
  - Functional Gastroduodenal Disorders,
  - Functional Bowel Disorders, and
  - Functional Abdominal Pain Syndrome
2. The absence of organic disease by appropriate investigations
3. Age ( $\geq 19$ ;  $\leq 70$  yrs),
4. No difficulty conversing in English
5. Sufficient symptom frequency, for  $\geq 3$ mo, to satisfy recent diagnostic criteria (see Appendix B)
6. Absence of major psychiatric or physical illness (eg. schizophrenia, severe diabetes)

Medications which patients have been taking for other conditions (eg. calcium channel antagonists, antidepressant medications, anticholinergics, and nonsteroidal

anti-inflammatory drugs (NSAIDS)), which may have conceivably produced a variety of GI symptoms, were always considered and excluded as a cause of patients' symptoms before enrolment into the study.

Differences in research questions across studies determined differences in the patient populations studied. Thus, for Studies 2, 3 and 5, patients with IBS (with and without FD) were specified, while for the evaluation of gastric emptying study (Study 3) the patient sample was required to have FD symptoms (with and without IBS). For Study 5, the effects of gender on jejunal motor activity and sensitivity were controlled by including women subjects only - for both the patient sample, and for the healthy control groups.

#### 2.1.2 SUBJECT RECRUITMENT

Every effort was made to ensure the smooth and consecutive recruitment of eligible subjects. While recruitment populations and procedures were standardised within each study, almost all subjects were recruited from the same general population of patients ie those attending for diagnostic endoscopic evaluation. For Studies 1 to 4, patients were recruited from the larger clinics of the Royal North Shore Hospital and the Mater Misericordiae Hospital. The patient sample for Study 5 was recruited from the Royal North Shore Hospital alone. Identification of potential participants was based in the first instance on the clinical diagnosis of the attending gastroenterologist. Initial contact with potential participants by a research nurse followed endoscopic evaluation and/or final confirmation of the diagnosis. That is, patients whose eligibility at endoscopy was confirmed by that procedure were invited to participate in the study. If additional clinical investigation was required, recruitment was postponed

until eligibility in terms of diagnosis was clear. At initial contact patients were advised in general terms about the nature of the study and in specific terms about important aspects of their involvement. They were assured of anonymity. Patients were advised that they would be approached to attend for interview with a research psychologist (the author) in the Department of Psychological Medicine, Royal North Shore Hospital or if this was not convenient, in the person's home. Recruitment was formalised at this latter interview with the patients' written consent.

### 2.1.3 RECRUITMENT STATISTICS

#### **Eligibility**

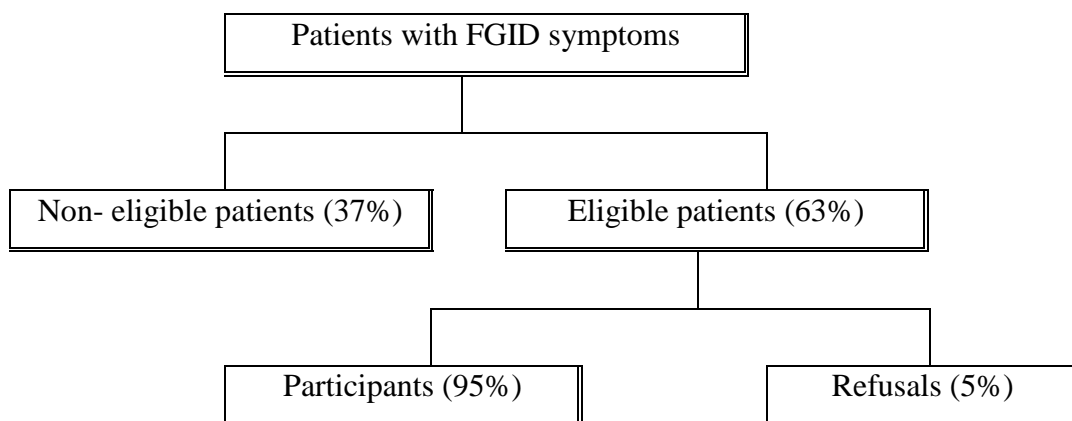
Thirty-seven percent of patients with FGID symptoms at endoscopy failed to meet the eligibility criteria for inclusion. The reasons recorded for their exclusion are summarised in Table 2.

TABLE 2  
PATIENTS FAILING TO MEET ELIGIBILITY CRITERIA

Reasons for Exclusion.	Percent of Total Sample
Insufficient criteria for a FGID diagnosis	6.6
Anorectal FGID only	3.0
Symptoms severely confounded by current medication eg NSAIDS	4.0
Age (<19yrs; > 70yrs)	12.6
Inadequate English	3.6
Major physical or psychiatric illness	6.0
unable to be contacted	1.2

## Response rate

Of the patients who were diagnosed with FGID symptoms following endoscopic evaluation who finally met the standard eligibility criteria, the majority agreed to participate (Figure 1). Ninety-five percent participated fully in the longitudinal and in the whole gut transit studies (Studies 1, 2, and 4) even though both studies required a substantial time commitment. The response rate for the gastric emptying study (Study 3) was also high with all patients agreeing to participate. Reasons for non-participation across all studies were time and/or major geographic constraints (2% and 3% respectively). The high participation rate for all studies was due, at least in part, to the care taken with subject recruitment procedures, and with all aspects of the person's continuing involvement. In total, 350 patients participated fully in one of the research projects.



**Figure 1** Overall eligibility and response statistics

#### 2.1.4 SUBJECT CHARACTERISTICS

This section describes salient features of the subject population as background information to the later discussion of the psychosocial predictors of gastrointestinal symptom and/or motility outcomes. This information, compiled from interview data and patient questionnaire responses, broadly describes the patient population with respect to age and gender, demographic characteristics, life stress characteristics (past, recent and present), and symptom characteristics.

##### **Age and gender**

The distribution of age and gender within the total patient population and across individual study populations is summarised in Table 3. The mean age of all participants was 43.5 ( $\pm$  13) years with a range of 19 to 74 years. Table 3 shows the distribution of age within each study sample to be generally consistent with the overall distribution. The majority of participants were women. The prominence of women within the total patient population reflects the pro-female distribution within the larger population (ie the proportion of FGID outpatients from whom these patients were recruited). Table 3 shows the overall female/male ratio for all participants to be 3.5 to 1. Gender distribution in the study subgroups varied around this ratio ranging from 2.1:1 (Study 3) to 4.8:1 (Study 4). By design, all patients and controls in Study 5 were women.

The potential for gender and/or age to influence symptom and motility outcomes, or to mediate significant relations between psychosocial factors and these outcomes, was considered *à priori*. Consequently, the potential for gender to influence jejunal motility activity and sensitivity influenced the decision to use a

gender homogeneous sample to determine normal and abnormal function in Study 5. In the mixed-gender studies, age and gender were assessed as independent predictor variables and/or as potential confounders of psychosocial-gastrointestinal relations. In this latter case their effects were controlled statistically.

TABLE 3  
AGE AND GENDER DISTRIBUTION IN EACH STUDY SAMPLE  
AND TOTAL SAMPLE

Study	Mean Age (SD) (yrs)	Age range (yrs)	F/M ratio
Study 1	44.0 (12)	19-70	2.5:1
Study 2	43.0 (12)	19-70	2.7:1
Study 3	44.1 (15)	19-74	2.1:1
Study 4	49.0 (15)	21-72	4.8:1
Study 5	42.0 (14)	20-68	All female
<u>Total patient population</u>	43.5 (13)	19-74	3.5:1

SD = standard deviation;  
F/M ratio = female/male ratio

### **Demographic characteristics**

An overview of the demographic characteristics of the patient population (Table 4) suggests that the patient sample represents a broad cross-section of the general population.

The majority of the sample was married or in a stable relationship (70%). Seventeen percent were single, 7% widowed, 4% separated and 2% divorced. Occupational status showed 50% in full-time employment, 17% were employed part-time, 21% worked at home, 4% were actively seeking employment, 5% had retired and 3% were full-time students. As almost all participants were either presently employed or had been employed in the past, the “highest” level of occupation was used as a socioeconomic indicator. The distribution of this indicator shows that participants came from the full range of economic strata (Table 4).

The formal education of participants in this study also spanned a broad range. Twenty-four percent had completed their education with one or more tertiary qualification, 32% had completed senior high school and/or completed further education in the form of a diploma or equivalent, and 44% had completed their formal education at or before the junior high school level.

### **Stress-related characteristics (past, recent and present)**

A personal psychiatric history was volunteered by 38% of the sample (Table 4). Most had sought professional assistance for depression (44%), anxiety (15%) or an anxious-dysthymic state (25%) while 6% had sought counselling for problems arising within the context of separation or divorce and an additional 10% for a major traumatic episode in the past. Sixty-two percent of participants reported no personal psychiatric history. It is noted that patients with major psychiatric illness were not eligible.

As well as a history of past stress-related problems, many of the patients in this study (98%) had recently been exposed to high levels of chronic life stress. Consistent with the pervasiveness of chronic stress within the patient sample, on

psychometric testing most patients had elevated levels of anxiety and/or very low or moderate levels of depression. It appears therefore, that for the majority of patients, anxiety and depression scores were more indicative of emotional distress than of a disorder of possible clinical significance. For some patients, however, anxiety and/or depression scores exceeded the threshold suggestive of clinical anxiety (7%) and/or clinical depression (30%).

### **Symptom characteristics**

Information concerning symptom onset (first time ever), the frequency and severity of current symptoms, and the duration of this symptom pattern prior to endoscopy was collected at interview. Diagnostic category and therefore number of concurrent categories was determined from questionnaire responses.

The participants varied broadly on each of these characteristics suggesting considerable heterogeneity of symptomatology within the patient sample (summarised in Appendix I). Onset of 'first ever' FGID symptoms varied from 6months to 50 years, symptom intensity scores for the previous 3 months ranged from 6 to 60, and the duration of this symptom pattern varied from 3 months to 240 months. The 50% cut-off point (median value) for these characteristics was 7 years for onset of first symptom, a score of 32 for symptom intensity, and 12 months for duration of present symptom pattern. The number of FGID syndromes to occur concurrently ranged from one to six, with a median value of two (Appendix I). The majority of patients (91%) however, had 3 or fewer syndromes, 7% had 4 syndromes and only 2% had five or six syndromes present concurrently.

**Table 4** Subject characteristics

Subject Characteristics	n = 350	%
<b>Sex</b>		
Female	252	72
Male	98	28
<b>Marital status</b>		
Married	245	70
Single	60	17
Widowed	24	7
Separated	14	4
Divorced	7	2
<b>Occupational status</b>		
Full-time	175	50
Part-time	60	17
Domestic duties	73	21
Unemployed	14	4
Retired	18	5
Student	10	3
<b>Highest level of occupation</b>		
Professional, Director	14	4
Semi-professional, manager, small business	45	13
Trades, nurse, teacher, administration	112	32
Semi-skilled, clerical, with responsibility	102	29
Unskilled with no responsibility	60	17
Never worked	17	5
<b>Education</b>		
University/college degree	84	24
Diploma or equivalent	70	20
Senior High School	42	12
Junior High School or less	154	44
<b>Personal psychiatric history</b>		
Yes	133	38
No	217	62
<b>Nature of psychiatric problem (n=133):</b>		
Anxiety	20	15
Depression	59	44
Anxiety-depression mixed	33	25
Divorce/separation	8	6
Major trauma / life stress	13	10

## **2.2 EXPERIMENTAL PROTOCOLS**

### **2.2.1 OUTLINE**

#### **All studies**

Psychosocial and symptom assessment involved (1) a semi-structured interview at the Royal North Shore Hospital or the person's home ie in comfortable, non-threatening surroundings at a time convenient to the subject, and (2) completion of psychological and symptom questionnaires (explained to the subject at interview, completed by the subject at home and returned by pre-paid post).

#### **Symptom-related studies**

Symptom assessment for Studies 1 and 2 involved (1) a semi-structured telephone interview to assess symptom intensity, constancy, and duration, and (2) completion of a symptom questionnaire (explained to the subject at the initial interview, completed at home and returned by pre-paid post). Telephone interviews were conducted independently of psychosocial assessments by the research nurse who made the initial contact with the subject.

#### **Gastrointestinal motility studies**

Gastrointestinal motility for Studies 3, 4, and 5 was also assessed independently of psychosocial assessments. The scintigraphic gastric emptying studies (Study 3) were performed in the Department of Nuclear Medicine, Royal North Shore Hospital, while the whole gut transit, motor activity and sensitivity

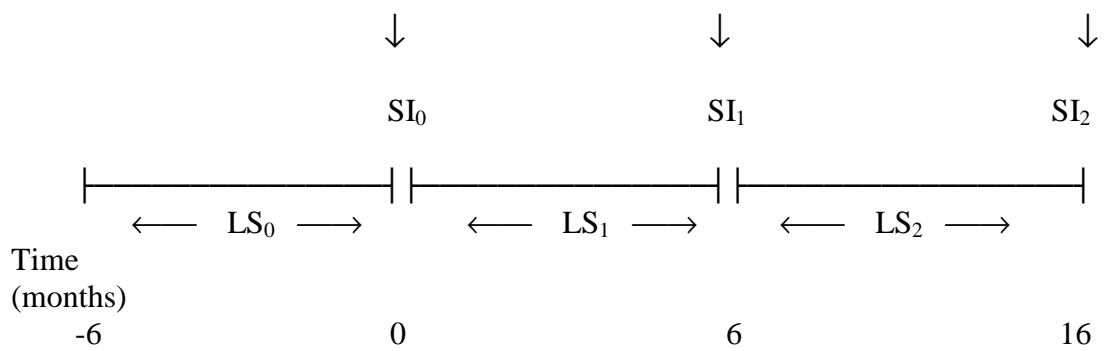
studies were performed in the Gastrointestinal Investigation Unit, Royal North Shore Hospital (Studies 4 and 5). Precautions were taken to ensure that the setting of the testing of gastrointestinal motor activity and sensitivity was as stress-free as possible. Stress levels were monitored as part of the research procedure to ensure that the findings reflected basal (non-stressed) levels. All measures satisfied this requirement.

Psychosocial, symptom, and motility data were collected and rated in an entirely blinded and independent manner throughout the studies.

#### 2.2.2 LONGITUDINAL DESIGN

Study 2 was designed to prospectively assess in patients with IBS (with and without FD) the relation of chronic life stress to symptom intensity over time. The longitudinal design is shown in Figure 2. Chronic life stress and symptom intensity were independently assessed at entry, 6 months and 16 months in a slightly staggered manner ie LS was assessed approximately two weeks before symptom intensity. Each time-frame allowed 6 months or more for each chronic stressor assessment.

All psychological measures to assess personality traits and anxiety were administered at entry only. The depression scale was assessed at entry and at 16 months. Diagnostic category (one or more FGID and/or a functional bowel disorder) was determined from patient responses on the Bowel Disease Questionnaire administered at 16 months as well as entry.



**Figure 2** Schematic illustration of the longitudinal study design.

LS = the average chronic threat intensity during the previous 6 months or more (=0), 6 months (=1) and 16 months (= 2); SI = the average symptom intensity during the following two weeks.

## **2.3 GASTROINTESTINAL SYMPTOMS AND MOTILITY ASSESSMENTS**

Conceptually, our research measures take into account both the nature and the course of IBS and FD. They consider both the use of standardised symptom-based diagnoses and the substantial overlap among FGID syndromes, among IBS and FD subgroups in particular. In practical terms, this means including a measure of the number of overlapping FGID subgroups present, assessing initial / baseline symptom intensity (and changes in symptom intensity over time) in patients with IBS by including the symptoms of FD as well as IBS. These measures are designed to reflect more accurately both the severity and the extent of the disorder within the GI tract. Similarly, with respect to transit, sensory, and motor function, attention is focused not only on the presence of an abnormality but the number of regions affected and the type and number of abnormalities present. These measures represent a novel approach.

### **2.3.1 DIAGNOSTIC CATEGORIES**

The diagnostic categories for all FGID are listed in Appendix A. Diagnostic categories were defined strictly according to criteria (based on the earlier Rome criteria), elaborated by Drossman and collaborators (1994). The criteria for diagnosis of the FGID used in this study are summarised in Appendix B. Classification of patients into these subgroups was determined from responses on the Bowel Disease Questionnaire (BDQ) (Talley et al, 1989b) after minor revision of questionnaire items to accommodate all of the above criteria. A recent version of the BDQ has been validated in an Australian population by Talley and colleagues (1995a).

Patients were diagnosed with FGID from three distinct classes of disorders - functional gastroduodenal disorders, functional bowel disorders and functional abdominal pain syndrome (see Appendix B). The subgroups assessed for this study included:

1. Functional Dyspepsia (FD), namely
  - a) ulcer-like (UL) dyspepsia,
  - b) dysmotility-like (DL) dyspepsia,
  - c) reflux-like (RL) dyspepsia<sup>a</sup>, and
  - d) unspecified (nonspecific) dyspepsia (UFD)
  
2. Functional Bowel Disorders (FBD), namely
  - a) irritable bowel syndrome (IBS),
  - b) functional constipation (FC),
  - c) functional diarrhoea (FDiar), and
  - d) unspecified functional bowel disorder; and
  
3. Functional Abdominal Pain Syndrome

<sup>a</sup> Reflux-like dyspepsia (defined as upper abdominal discomfort, plus heartburn and/or regurgitation at least once a week, for 3 months or more) (Drossman et al, 1990a) was also included because these latter symptoms frequently overlap with ulcer-like and dysmotility-like dyspepsia and with IBS.

The appropriate subgroup classification was determined by the initial contact research nurse who was unaware of the psychosocial data. An *à priori* decision was taken that aerophagia and functional abdominal bloating could not be diagnosed readily from questionnaire responses alone; these subgroups were therefore not included. Apart from those FGID subgroups which were by definition mutually exclusive, independence among subgroups for the purpose of diagnosis was assumed *à priori*.

### 2.3.2 GASTROINTESTINAL SYMPTOMATOLOGY

A semi-structured interview assessed the intensity, the constancy and the duration of GI symptoms.

#### **Symptom intensity**

The intensity of current FD and IBS symptoms was defined as the product of the frequency and the severity of each of fourteen IBS/FD symptoms during the previous two weeks (see Appendix J). Each dimension was graded on a 4-point scale. Frequency was scored on a scale of 0 - 3, where 0 = not a problem, 1 = occurred once only in the two week period, 2 = occurred more than once each week, and 3 = occurred almost every day, or daily. Severity was also scored 0-3, where the rating was 0 if this symptom had not occurred, and where 1 = mild severity (no remedy sought, no remedy tried), 2 = moderate severity (remedy sought, but daily activities were not effected), and 3 = severe (interfering with daily activities). Symptom intensity was assessed at consultation in all studies, and at entry, 6 months and 16 months in the longitudinal study (Study 2).

### **Symptom constancy**

The constancy of 'upper' and 'lower' abdominal pain and discomfort in FD or IBS was assessed for the previous two weeks on a 5-point scale where 1 = episodic (discrete, infrequent bouts); 2 = periodic remissions (> 1 month between brief bouts); 3 = constant (>3 bouts per fortnight); 4 = constant daily; and 5 = always present, day and night. Symptom constancy was assessed at entry only.

### **Symptom duration**

The duration of this pattern prior to presentation for endoscopy was assessed in months.

#### **2.3.3 EXTRAINTESTINAL (SOMATIC) SYMPTOMS**

A modified version the Psychosomatic Symptom Checklist (Talley et al, 1989b) was used to ascertain the presence (> 25% of the time during the past 3 months) of concurrent extraintestinal symptoms (EIS) namely fatigue, tension headaches, migraine headaches, unpleasant taste, nocturia, urinary frequency/urgency, incomplete bladder emptying, dry skin (eczema-like), insomnia and backache. Several habitual behaviours were also assessed during the interview procedure, including binge-eating (Crowell et al, 1994). No patient fulfilled the criteria for bulimia nervosa, and none had used inappropriate compensatory behaviours (eg. self-induced vomiting) during the current FGID episode or for at least the previous 6 months.

#### 2.3.4 TECHNIQUES TO ASSESS SENSORIMOTOR FUNCTION

Methods, employed to assess gastrointestinal motility for Studies 3, 4 and 5, are outlined in detail in Appendices K, L, and M respectively. In brief, gastrointestinal motility dysfunction in various regions of the digestive tract was determined using:

1. a standard dual-isotope scintigraphic technique to assess solid and liquid gastric emptying, employing power exponential analysis (Study 3),
2. a novel wholly scintigraphic technique for assessing whole gut transit which enabled assessment of all three regions of the gut simultaneously - that is, the stomach, the small intestine and the colon (Study 4), and
3. standard techniques to assess motor and sensory abnormalities
  - a) 24-hour ambulant duodenojejunal (small bowel) manometry to assess motor activity, both during fasting (phases 2 and 3 of the migrating motor complex (MMC)) and postprandially; and
  - b) balloon distension to assess jejunal sensitivity (Study 5).

#### 2.3.5 MOTILITY OUTCOME VARIABLES

The psychosocial and demographic concomitants of gastrointestinal motility dysfunction were determined using the outcome variables so derived, namely (see also Appendices K, L, M):

### **Study 3: Evaluation of gastric emptying in FD**

Scintigraphic parameters of solid and liquid emptying:

- Solid delay time (defined as the time to 2% emptying)
- Solid  $T_{1/2}$  (time for 50% of solid emptying)
- Rate of emptying (% / minute) of solid at 45 minutes
- Rate of emptying (% / minute) of solid at 70 minutes
- Liquid lag ( $\beta$ ) (a parameter defining the shape of both solid and liquid curves)
- Rate of emptying of liquids at 45 minutes.

### **Study 4: Evaluation of whole gut transit in FGID**

Scintigraphic parameters of gastric emptying, small intestine transit and colonic transit:

- Gastric emptying parameters as in Study 3
- Small intestinal transit time (defined as the time from 50% gastric emptying to 50% caecal filling)
- Colonic transit  $T_{1/2}$  (time for 50% colon emptying)
- Patient subgroups based on the presence of delayed gastrointestinal transit, where delay was defined as one or more scintigraphic parameters below the 5<sup>th</sup> centile of the normal range, in each region:
  - i. Delayed gastrointestinal transit in one region
  - ii. Delayed gastrointestinal transit in two regions
  - iii. Widespread delay in transit (delay in two or more regions)
  - iv. Normal transit in all three regions

## **Study 5: Evaluation of jejunal sensorimotor function in IBS**

Parameters of sensitivity and motor activity:

- Hypersensitivity (defined as heightened sensitivity to balloon distension where hypersensitivity was defined as balloon distension volumes below the 25<sup>th</sup> centile for the normal range of balloon volumes):
  - i. for initial perception, and
  - ii. for pain threshold
- Motor activity abnormalities (defined as abnormal fasting small bowel motor activity (abnormal phase 2 or phase 3 of the migrating motor complex) and/or abnormal postprandial small bowel motor activity, if any parameter relevant to that phase was outside of the normal range for that parameter). See section 2.5 for information relevant to the establishment of the normal ranges for our laboratory).
- Patient subgroups based on the presence of sensory and/or motor abnormalities:
  - i. Sensorimotor subgroup  
(defined as the presence of heightened perceptual and pain sensitivity, abnormal postprandial and fasting motor activity)
  - ii. Motor subgroup  
(defined as normal sensitivity, abnormal postprandial and fasting motor activity), and
  - iii. Fasting motor subgroup  
(defined as normal sensitivity, normal postprandial motor activity and abnormal fasting motor activity).

## 2.4 PSYCHOSOCIAL ASSESSMENTS

Both interview and questionnaire methods were employed to gather objective and reliable information relevant to the social (life stress, emotional support) circumstances of patients with FGID, their personality, and their coping style. The life stress variables reflect the quality, severity and duration of recent and/or current life stressors. The distress/mood state variables represent the severity and extent of affective (anxious and depressive) symptomatology while other variables reflect specific aspects of personality and coping style. Each is relevant to stressful experiences and responses that existing evidence suggests may contribute to the development and/or exacerbation of IBS/FD symptoms, perhaps through specific pathophysiological mechanisms such as sensory and/or motor abnormalities. For reference purposes a summary of the psychological and social predictor variables and their use in each of the five studies is presented in Table 5. At all levels, these data were collected and processed independently of the collection and processing of gastrointestinal symptom and motility data.

### 2.4.1 SEMI-STRUCTURED INTERVIEW

This gathered information relevant to life stressors and intimate emotional support.

#### **Social stressors**

The Life Events and Difficulties Schedule (LEDS) (Brown & Harris, 1978) was used to elicit detailed information, during an interview of approximately two

hours duration, about *discrete life events and chronic difficulties* (defined as 6 months or more) that were current during the previous 6 months - their onset, duration, type, intensity (in terms of provoking a strong emotional response such as fear, flight or fright, anger or frustration) and broad social context. *Biographical or personal information* (eg. adoption, child abuse, immigration, multiple miscarriages etc) of relevance to the particular *meaning* of the stressor (ie what was at stake for an individual in those circumstances), was also recorded. With no reference to the subject's *own* emotional response, these objective (externally verifiable) data were presented by the interviewer in vignette form to an experienced rater. In essence, the stressor rating provides a measure of the degree of *threat* innate in the circumstances (ie to the person's security, future well-being or personal integrity etc.) and the degree of *goal-frustration* such a happening may have provoked (eg. by obstructing specific personal aims, needs and ambitions).

Clinical validity and reliability have been established for the LEDS method (Tennant et al, 1979) and inter-rater reliability is high (Tennant et al, 1979). Only stressors that were judged to be independent of FGID symptoms were coded for analysis. Each stressor was rated separately for emotional threat and for goal frustration on a four-point scale where 0 = mild; 1 = moderate; 2 = severe and 3 = very severe. For each individual, the threat and goal-frustration components of each stressor may differ considerably. Measures of chronic *threat* were both *dichotomous* (the presence or absence of at least one chronic stressor that was highly threatening), and *continuous* (a 'total chronic threat' score - namely, the sum of the chronic threat ratings across all chronic stressors). Similar variables were derived from stressor ratings of chronic *goal-frustration*.

In addition to the life stress variables used in previous studies of FGID (Craig & Brown 1984; Bennett et al, 1991), two global chronic stressor scores were calculated for each patient: a *total chronic threat score* (the sum of the threat ratings across all chronic stressors) and a *total chronic goal frustration score*.

For the longitudinal study (Study 2), only chronic stressors (of at least 6 months duration) were included in the analyses, ie stressors of short duration (< 6 months duration) were excluded. Each chronic stressor rated as severe and likely to be *independent of IBS/FD symptoms and psychiatric illness* was included. In the context of this study, each stressor rating represented the *average* severity of threat/goal-frustration for at least 6 months prior to each assessment. In all, twelve LS variables - four (two threat and two goal-frustration: one dichotomous, one continuous) - for each assessment point (entry, 6 months, 16 months).

### **Intimate emotional support**

Utilizing the interview, vignettes and ratings, the *availability* and *quality* of intimate emotional support was recorded for intimate persons in the social network. Firstly, the availability (presence or absence) of an intimate person was established, and the quality of emotional support was rated as good, adequate or poor. These dimensions were then collapsed into one dichotomous 'quality of intimate emotional support' variable, where 0 = the presence of adequate or good emotional support, and 1 = an absence of, or poor quality emotional support. The reliability of this interview-based method of emotional support assessment has been established (Henderson, 1980).

#### 2.4.2 PSYCHOLOGICAL QUESTIONNAIRES

This self-report method was used to provide *psychological* data. Questionnaires assessed several broad psychological domains, namely emotional distress, personality and coping; each domain of particular relevance to hypothesised links between psychological disturbance and the nature, severity and extent of gastrointestinal symptoms and motility disturbances (Table 5). Selection of measures was based on the ability of each set of questions to reliably measure one or more variable of interest with as little overlap between psychological and gastrointestinal disturbances as possible. The development and properties of each questionnaire are reviewed in the context of their relevance for this project.

Measures used extensively in the literature (eg The State-Trait Anxiety Inventory (STAI)) are not included in the Appendix.

##### **Emotional distress / current mood state**

The extent of current depressive and anxious symptomatology were assessed using separate self-report measures.

##### Depression

The Centre of Epidemiological Studies Depression Scale (CES-D) (Radloff, 1977) was developed by the Center for Epidemiological Studies, National Institute of Mental Health (NIMH), for use in studies of depressive symptoms in the general population. It was designed to measure current levels of depressive symptomatology with particular emphasis on the affective component, depressed mood. It has been

**Table 5** Summary of psychological and social variables per study

<u>Psychological Variables</u>	<b>Primary Outcomes:</b>				
	<b>Symptom-related</b>		<b>Gastrointestinal Motility</b>		
	Study 1	Study 2	Study 3	Study 4	Study 5
<b>Emotional distress/ mood state</b>					
Depression	x	x	x	x	x
Anxiety	x	x	x	x	x
<b>Personality and coping style</b>					
Trait anxiety	x	x	x	x	x
Extroversion	x	x	x	x	x
Neuroticism	x	x	x	x	x
Trait anger					
Anger temperament	x	x		x	x
Anger reactivity	x	x		x	x
Other trait anger	x	x			
General Hypochondriasis	x	x		x	x
Defense Style					
Immature	x	x		x	x
Mature	x	x		x	x
Neurotic	x	x		x	x
Locus of Control of Behaviour			x		
Self not in control	x	x			x
External factors in control	x	x			x
Need help	x	x			x
Emotional expression/ suppression					
Anger held-in	x	x	x	x	x
Anger expressed	x	x	x	x	x
Anger controlled	x	x	x	x	x
Anger suppressed	x	x	x	x	x
Anxiety suppressed	x	x	x	x	x
Depression suppressed	x	x	x	x	x
Mental adjustment to chronic stressor					
Fighting spirit			x		
Helpless-hopelessness			x		
<b>Life stressors /chronic difficulties</b>					
One or more high in threat	x	x			
One or more high in goal-frustration	x	x			
Total chronic threat score	x	x			
Total chronic goal-frustration score	x	x			
<b>Intimate emotional support</b>					
Quality (absent/poor v adequate/good)	x	x			

shown to be a sensitive tool for detecting depressive symptoms and change in depressive symptoms over time in psychiatric populations (Weissman et al, 1977). Subsequent to its development, the CES-D has been most commonly applied to the exploration of relations between depressive symptomatology and other characteristics in general, medical and psychiatric populations.

The CES-D is a 20-item self-report measure, 16 items describe negative symptoms, four are stated in a positive direction (and subsequently reversed). Each item is rated on a scale of zero (rarely, not at all,) to three (most of the time) rating. Respondent are asked to indicate how they felt during the past week. When all items have been summed scores can range from zero to 60. The total score is used as an estimate of the degree of depressive symptomatology. Re-test scores are used to indicate the extent of change in depressive symptoms over time.

Self-report symptom scales are not intended as diagnostic instruments. Nevertheless, they can function with modest accuracy to screen for possible or probable 'cases' of depression (Boyd et al, 1982). In this study the cut-off threshold of 17 was used to estimate possible 'cases' (Boyd et al, 1982).

The CES-D was chosen to assess the degree of depressive symptomatology and change in depressive symptomatology over time in this large sample of patients with FGID who otherwise appear to be representative of the general population. The affective component - a depressed mood state - suited the purpose of relating depressive symptomatology to other (gastrointestinal and extraintestinal) symptomatology within the context of high levels of life stress. Each item of the CES-D was independent of FGID diagnostic criteria and extraintestinal symptoms.

## State anxiety

The State-Trait Anxiety Inventory (STAI) of Spielberger and collaborators, (Spielberger et al, 1970) was constructed to provide brief, internally consistent, reliable and valid self-report scales for assessing state and trait anxiety in a variety of populations and settings. It comprises two separate psychometric scales for measuring two distinct but related anxiety concepts - the concept of transient emotional arousal which fluctuates as a function of stressful situations (state) and a more stable anxiety-proneness factor (trait). State anxiety is discussed in this section.

For more than 20 years, the STAI has been one of the most widely used of the self-report measures of subjective anxiety. Two versions have been used extensively. In this study the original scale (Form X) was used in Study 3. The revised version (Form Y) was chosen for the other four studies. In the revision process, six items on each scale that were more closely related to depression than to anxiety were replaced, and the wording of several items was simplified (Spielberger et al, 1983a). The psychometric properties of the replacement items were maintained or improved by these changes ie factor loading or item-remainder correlations, or both, were larger. This measure of state anxiety is slightly more 'pure' - that is, one that is more independent of depression and more specifically a measure of *current levels of tension and apprehension*.

The STAI state anxiety scale consists of 20 statements that ask respondents to report how they feel at that particular moment by rating the intensity of their subjective feelings of anxiety (eg. "I feel frightened") on the following 4-point scale: (1) not at all, (2) somewhat, (3) moderately so, and (4) very much so. For 10 items a

rating of 4 indicates the *presence* of a high level of anxiety (eg. “I feel upset”), for the remainder a high rating indicates the *absence* of anxiety (eg “I feel calm”). The scoring weights for the anxiety-absent items are reversed before the items are summed. The scale minimum and maximum are 20 and 80 respectively.

The revised test manual (Spielberger et al, 1983a) includes validity and normative data. In brief, both STAI scales are highly satisfactory in terms of internal consistency, stability (stable for the trait measure, changeable for the state measure), and concurrent validity. For descriptive purposes only, the threshold score of 57 (85<sup>th</sup> percentile rank among general medical patients; Spielberger et al, 1970) can be used to estimate probable ‘cases’.

The STAI (Form Y) was the anxiety scale of choice for this study. It has been used increasingly in investigation of stress-related medical and psychiatric disorders. As a valid measure of current levels of tension and apprehension, it complements the CES-D measure of depressive symptoms. The inclusion of both measures allows the simultaneous assessment of two dimensions of a current (transitory or prolonged) mood states in patients with FGID.

## **Personality**

Structured questionnaire measures assessed five aspects of personality, namely trait anxiety, extraversion - introversion, neuroticism, trait anger and general hypochondriasis.

## Trait Anxiety

In this section, discussion of The State-Trait Anxiety Inventory (STAI) of Spielberger - Form X (1970) and Form Y (1983a) - will be confined to the trait anxiety measure alone. The Form Y version of this measure, which focussed wholly on the symptoms of anxiety, is even more specific as a measure of relatively stable differences in *anxiety-proneness (trait)*. That is, the measure more finely assesses differences in the tendency of individuals to perceive or appraise stressful situations as personally dangerous or threatening and to respond to such situations with elevated *state* anxiety.

The instructions for this trait anxiety scale asks respondents to report how they *generally feel* by rating *how often* they have experienced particular symptoms of anxiety (eg. “I worry too much over something that really doesn’t matter”) on the following 4-point frequency scale: (1) Almost never, (2) Sometimes (3) Often, and (4) Almost always. For eleven items, a rating of four indicates frequent high levels of anxiety (eg in relation to experiencing disturbing thoughts). For nine items a high rating indicates that anxiety is generally *absent* (eg in relation to feeling calm). The scoring weights for the anxiety-absent items are reversed before the items are summed. The scale minimum and maximum are 20 and 80 respectively.

As a valid measure of anxiety proneness the STAI (Form Y) measure of trait anxiety was selected as entirely appropriate in the context of this study.

## Extraversion and neuroticism

The Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975) is a development of various earlier personality questionnaires designed to measure two major dimensions of personality - extraversion and neuroticism. This 90-item version also includes a subscale for psychoticism, and a lie scale. Using the method of Latent Trait Model (LTM) analysis (Grayson, 1986), short forms of 10-items length, were derived from this 90-item EPQ instrument for each of the four factors. This powerful new technique for questionnaire analysis essentially seeks to identify the 'best' items on a questionnaire, that is, those that most accurately identify the construct being measured. This approach provides precision of measurement in ways not previously available (Grayson, 1986). These short forms were used to measure extraversion-introversion (see Appendix N) and neuroticism (see Appendix O) in this study.

Extraversion and neuroticism are firmly established theoretically and empirically as stable constructs of personality. Individually and together, they contribute substantially to the description of a person's personality (Eysenck & Eysenck, 1975). High scores on *extraversion* describe a person who tends to be outgoing, has many social contacts, has 'party-stirring' abilities, may be fairly easy-going and uninhibited, often impulsive and aggressive, and not always reliable. High scores on *introversion* describe a quiet, retiring sort of person, introspective and generally reserved, distant except with intimate friends, someone who likes to be organised and plan ahead, is quite serious, seldom behaves aggressively and is not prone to bouts of temper. High scores on *neuroticism* or 'emotionality' describe a person who is a 'worrier'. This person is often anxiously preoccupied with things

that may go wrong, tends to be moody and overly emotional, prone to react too strongly to all sorts of stimuli and to calm down slowly following each arousal.

The strong influence of heredity on extraversion and neuroticism has been shown in several studies. For example, Shields (1962) found that identical twins brought up separately correlated very highly on both extraversion and neuroticism (more than fraternal twins and even more than identical twins brought up together). Physiologically, the neuroticism factor is closely related to the inherited degree of lability of the autonomic nervous system, while the extraversion-introversion factor is closely related to the degree of excitation and inhibition prevalent in the central nervous system, the balance of which may be mediated by the ascending reticular formation (Eysenck & Eysenck, 1985). The basic tenet underlying the development of the EPQ (or similar) is that, in interactions with the environment, observable behaviour is a function of constitutional differences in the excitation / inhibition balance. EPQ questions are designed to tap observable (phenotypic) behaviours which arise from these interactions; questions that tap physiological responses suggesting autonomic arousal are not included. On balance, genetic factors appear to contribute more than environmental factors, to individual differences in personality (Eysenck & Eysenck, 1985).

Evidence directly supports the validity of these measures as stable descriptions of observable behaviours over time. It also supports the independence of extraversion and neuroticism as measures of distinct and unrelated aspects of personality. Test-retest reliability using single or parallel forms is high (more than 0.85 even after several months). Studies using nominated (criterion) groups - individuals independently judged as extroverted, introverted, stable and unstable - attest to the validity of scores on these measures as reasonably valid pictures of

observed behaviour patterns. The relation is particularly strong in groups with extreme tendencies. In support of the conceptual independence of extraversion and neuroticism, scores on these scales are almost entirely orthogonal in both normal and patient groups (Eysenck & Eysenck, 1975).

Given that extraversion and neuroticism tend to predispose to more intense and prolonged stress responses, the short-form EPQ was used in this case to assess the relation of extraversion and neuroticism to the number and type of FGID syndromes present and to gut function in FGID - also, the extent of their influence as mediators of relations eg between social factors (life stress, emotional support) and symptoms intensity (Study 2).

#### Trait anger

To assess individual differences in *anger proneness* as a personality trait, the 10-item trait anger scale of The State-Trait Anger Scale (Spielberger et al, 1983b) was used. This scale is analogous in conception and similar in format to the STAI (Spielberger, 1970; Spielberger et al, 1983a). Thus the concept of *trait* anger is distinguished from *state* anger (ie angry feelings that vary in intensity and tend to fluctuate over time in reaction to stressful situations). Trait anger is defined in terms of individual differences in the *frequency* of anger experiences over time. Within this conceptual framework, it is assumed that persons with high trait anger are more likely to perceive a wide range of situations as anger-provoking (eg annoying, irritating, frustrating), and to respond to such situations with elevations in state anger; their responses may also be *more intense* in such circumstances.

In the construction of this instrument only items specific to the phenomena of angry feelings were considered. Spielberger and colleagues (1983b) were careful to differentiate this more ‘fundamental’ concept from similar, more complex phenomena such as hostility and aggression. The trait anger items selected were administered to a sample of 146 college students and subsequently to 270 Navy recruits. The rating scale format and administration procedures for trait anger were the same as those used for the trait anxiety scale ie respondents were asked to rate “how you generally feel” on a 4-point scale of (1) Almost never; (2) Sometimes, (3) Often, (4) Almost always. Based on the item-remainder correlations (the highest), and correlations with anxiety (the lowest), a 10-item scale was constructed. The 10-item short form, very useful because of its brevity, provided essentially the same information as the longer form, with the additional advantage that overlap with trait anxiety was greatly reduced.

Factor analysis yielded a two-factor solution for both males and females. Four items had high loadings on each of these factors, with low loadings on the other. On the basis of their content, the factors were labelled Angry Temperament and Angry Reaction.

The *trait anger temperament* items describe individual differences in the disposition to express anger, without specifying any provoking circumstances:

“I have a fiery temper”

“I am quick-tempered”

“ I am a hot-headed person”

“I fly off the handle”

In contrast, the *trait anger reaction* items describe anger responses in situations that involve frustration and/or negative evaluations:

“It makes me furious when I am criticised in front of others”

“I get angry when I’m slowed down by others mistakes”

“I feel infuriated when I do a good job and get a poor evaluation”

“I feel annoyed when I am not given recognition for good work”

The loadings of the two remaining items were spread across both factors. These *Other Trait Anger* items appear to describe reactions when someone feels angry or frustrated, but do not specify the anger-provoking circumstances:

“When I get mad, I say nasty things”

“When I get frustrated, I feel like hitting someone”.

Given the small number of items in each 4-item subscale, internal consistency was high.

The development and validation of this psychometric instrument for the assessment of anger is described in detail by Spielberger and collaborators (1983b). Research findings based on efforts to validate The State-Trait Anger Scale are also reported.

The phenomenon of anger as a personality trait in FGID has received little attention. Individual differences in *angry temperament* and *angry reaction* may be relevant to FGID symptoms and motility; this has not been assessed.

### General hypochondriasis

Hypochondriasis was assessed using one of the seven subscales of The Illness Behaviour Questionnaire (IBQ) of Pilowsky and Spence (1983) namely, *General Hypochondriasis*. The IBQ was developed to assess various aspects of illness behaviour - in particular, attitudes that suggest inappropriate or maladaptive modes

of responding to one's state of health where there is a fundamental discrepancy between the objective pathology present and the patient's response to it. Hypochondriasis lies within the general framework of *abnormal illness behaviour* (Pilowsky, 1969). The specific focus of the 9-item General Hypochondriasis factor is phobic concern about one's state of health. These concerns are associated with arousal or anxiety but also with some insight into the inappropriateness of these illness-related attitudes. Interpersonal discord may also be reflected in responses, however this is secondary to the person's phobic concern. Hypochondriacal concerns range from common short-term worries to persistent and distressing fears or convictions of having a disease.

The IBQ Manual (Pilowsky & Spence, 1983) outlines the development of the IBQ and provides information regarding norms, utility, reliability and validity. The general hypochondriasis factor has significant test-retest reliability (correlation of 0.87,  $p = 0.001$ ), good spouse-patient correlation agreement (0.5,  $p = 0.002$ ), and criterion group discriminative validity (scores discriminated in the predicted direction: mean scores for pain patients fell between general practice patients who had the lowest scores, and psychiatric patients who had the highest scores). The 9-item General Hypochondriasis Scale is presented in a forced-choice format (see Appendix P).

It is anticipated that hypochondriacal concerns will be generally elevated within this patient sample. Given the difficulty of providing a satisfactory explanation for FGID symptoms, it is likely that even after medical reassurance, the continued presence of gastrointestinal symptoms will remain worrisome for at least some patients. Individual differences in the effects of these concerns on symptomatology and motility are relevant to research in this area.

## **Coping style**

Coping style was assessed in terms of emotion-focussed coping (defense style), problem-focussed coping (locus of control of behaviour), coping with anger (its expression, suppression and control), coping with unpleasant mood states (anxiety, depressed mood and anger) and with a 'real-life' chronic stressor (fighting spirit, helplessness/hopelessness).

## Defense Style

The Defense Style Questionnaire (DSQ 40) (Andrews et al, 1993) was developed to reliably assess specific aspects of defense style, the use of *mature*, *immature* and/or *neurotic* defenses (see Appendix Q). The DSQ purports to measure relatively stable manifestations of an individual's habitual style of dealing with conflict - both conscious, and unconscious. A strong correspondence between self-report scores on the DSQ (Bond et al, 1983) and clinical assessments of defenses (Vaillant et al, 1986) supports the underlying assumption that endorsement of certain attitudes and beliefs can be taken as reflecting the habitual use of the defense. The DSQ 40 can yield both 20 individual defense scores and three higher-order factor scores (mature, immature, neurotic). Four defenses correspond to the mature factor (sublimation, humour, anticipation, and suppression), four to the neurotic factor (undoing, pseudo-altruism, idealisation, and reaction formation), and twelve to the immature factor (eg projection, passive aggression, acting out, isolation, denial, splitting, etc). The predictive value of the higher-order factor scores is the primary focus in this study.

Subsequent to the measurement of defense style by time-consuming interview-based methods (Vaillant, 1976), the DSQ self-report instrument was constructed (Bond, et al, 1983) and refined (Andrews et al, 1989; Andrews et al, 1993). Important refinements include relabelling of defenses in terms of DSM-III-R defense mechanisms (Andrews et al 1989), reducing the size of the questionnaire (Andrews et al 1989), the removal of 'symptom' items (Andrews et al, 1993), and based on eight statistical and two a priori criteria the choice of two items to represent each of the 20 defenses. During the latter process, the heterogeneity of the defenses was preserved in the factor scores (mature, immature, neurotic), while internal consistency was preserved at the level of the individual defenses (eg humour, undoing, projection).

Normative and reliability data, based on scores derived from patient (anxiety disorder, child-abuse parents) and non-patient (healthy control) groups (Andrews et al 1993), suggest that the instrument possesses reasonable psychometric properties, including internal consistency and temporal stability appropriate in a trait measure - 38% of which can be attributed to genetic factors, 62% to environmental factors (Andrews et al, 1993). The new DSQ 40 compares well with the longer 72-item version, with correlation coefficients of 0.97, 0.95 and 0.93 for the mature, immature and neurotic factor scores respectively (Andrews et al, 1993). The DSQ 40 however, has proven to be the more discriminating measure, identifying with improved precision the primary discriminating factor - mature defenses. That is, while both versions significantly discriminated among anxiety patients, child-abuse parents and normal controls, in the absence of symptom items (DSQ 40) the contribution of the mature factor superseded the contribution of immature and neurotic defenses.

Inclusion of defense style on this occasion reflects the importance placed in this study on individual differences in the way people with FGID cope with stress, and whether differences in the maturity of defense style (a relatively stable characteristic) can predict the nature, severity and/or extent of functional gastrointestinal symptomatology and motility disturbance.

#### Locus of control of behaviour

The Locus of Control of Behaviour (LCB) was developed to measure perception of personal control in a clinical context - in particular, in relation to the personal control of unwanted behaviour (Craig et al, 1984). The concept refers to the extent to which a person believes that personal efforts, more than external factors (such as other persons, uncontrollable circumstances, or chance) can achieve a positive outcome. These beliefs are subject to change over time and altered circumstances.

The original LCB is presented in a 17-item six point bipolar Likert-type format. It has satisfactory internal reliability, test-retest is reliable in the absence of treatment, it is independent of age, gender and social desirability, and it discriminates between normal healthy subjects and those with neurotic disorder. A low score on this instrument indicates a strong belief in personal control. Those who score higher tend to believe that their personal efforts are generally futile. The sensitivity of the LCB as a tool to assess change in locus of control over time has been demonstrated. Craig and colleagues (1984) found that, during a treatment program for stuttering, no change or an increase towards the external dimension predicted a performance deficit or relapse in the condition in the long term. It appears that for some individuals, attribution style (ie failure to attribute improvement to self-efforts)

inhibited the development of more effective problem-focussed coping strategies for this behaviour in the long term. This early version of the LCB was used in Study 3 only.

Subsequent changes to the LCB (Andrews et al, 1990) - the removal of three items which confounded with symptoms of anxiety - made the 14-item measure (see Appendix R) even more appropriate for use in Studies 1, 2 and 5. Factor analysis of the responses of a large population of twins (N = 924, females = 54% mean (S.D.) age = 34 (11) yielded 3 interpretable factors which were called: (1) *self not in control* (Items 1,5,12,13), (2) *random factors in control* (Items 2,3,10,14), and (3) *need others help for control* (Items 4,6,11). Normative data from this non-clinical population are available (from the above authors - Andrews et al, 1990). This study is one of the first to assess these factors in a clinical sample.

The Locus of Control of Behaviour Scale was chosen to determine whether perception of personal control is associated with emotional distress levels, the number of FGID present, symptom intensity and the severity and extent of sensorimotor and transit abnormalities. Based on Craig's findings, one might expect perceptions of personal control (self-efficacy expectations) to be lower among patients with the most severe and chronic disorder.

#### Anger expression / suppression

The Anger Expression (AX) Scale (Spielberger et al, 1987) assesses a component of anger - *anger expression*, that is distinct from the state-trait aspects of anger experiences. The AX scale was constructed to assess how people *generally react or behave* when they feel angry or furious. More specifically, it was developed to assess individual differences in the extent to which people express anger overtly or

directly, how frequently they hold in or suppress angry feelings, and the extent to which they attempt to control or resist becoming angry. These differential reactions to feelings of anger are measured by three 8-item subscales of the 24-item AX scale (Spielberger et al, 1987). Each subscale, loaded on one dimension, assesses the tendency:

- (1) to express anger towards other people or objects in the environment (*Anger-out*) - for example, 'I do things like slam doors', 'I argue with others', 'I loose my temper',
- (2) to experience, but hold in (suppress) angry feelings (*Anger-in*)  
- for example, 'I keep things in', 'I am angrier than I am willing to admit', 'I boil inside, but I don't show it', and
- (3) to control and/or resist becoming angry (*Anger-control*)  
- for example, 'I control my angry feelings', 'I keep my cool', 'I am patient with others', 'I try to be tolerant and understanding'.

Anger-out and Anger-in are empirically independent, factorially orthogonal dimensions that have demonstrated validity and reliability (Spielberger et al, 1985; Mills et al, 1989; Knight et al, 1988). The psychometric properties of the 8-item Anger-control subscale (it previously comprised only three items; Spielberger et al, 1985) have not been as well researched, particularly since the addition of the new items (Knight et al, 1988). The new AX scale (1987) and the previous scale (1985) differ only in the number of items in the Anger-control subscale (eight and three respectively).

In assessing different styles of anger expression, the AX scale unambiguously complements the frequency of anger experiences (trait). The physiological effects of

suppression of anger on autonomic, neuroendocrine, and digestive functioning underlies the inclusion of these anger dimensions in this study.

### Suppression of emotions

The Courtauld Emotional Control Scale (CECS) was developed by Watson and Greer (1983) to measure specific aspects of the psychological construct emotional control - the suppression of anger, anxiety and unhappiness (depressed mood). The CECS complements (and slightly overlaps) the dimensions of anger assessed by the AX, by providing subscales which are designed to assess the extent to which individuals suppress their reactions when they feel angry, anxious and/or sad. Subjects respond on a 4-point frequency scale, graded from “almost never” to “almost always”, how they *generally react* when they feel *angry* (very annoyed), *anxious* (worried) and *unhappy* (miserable). Each of these affective responses is assessed separately on a 7-item subscale which includes positive statements in the direction of suppression of emotions (eg ‘I hide my annoyance’ ‘I refuse to argue or say anything’, ‘I keep quiet’, ‘I bottle it up’) and in the opposite direction (eg ‘I let others see how I feel’, ‘I tell others about it’ and ‘I say what I feel’). These latter scores are subsequently reversed. Higher total scores on each subscale indicate greater suppression of anger, anxiety and/or depressed feelings. A total *control of emotion* score can be obtained by summing across all three subscales. The more interpretable subscale scores were selected over and above the global score as predictor variables for this study.

The psychometric properties of this scale have been tested, and reliability and validity established among nonpatient (eg hospital employees) and patient (eg breast cancer) groups (Watson & Greer, 1983; Pettingale et al, 1985). For example, CECS

scores were found to be independent of social desirability bias (assessed by the Marlowe-Crowne scale) while a significant inverse relation between emotional control and type 'A' behaviour (assessed by the Bortner Scale) supported the validity of the emotional control construct as measured by the CECS.

Although originally intended for use with breast cancer patients, the CECS has been used widely in psychosomatic research. The CECS was used in this study to assess the relation of suppressed anger, suppressed anxiety and suppressed unhappiness to the severity and extent of functional gut symptomatology, transit and sensorimotor dysfunctions.

#### Mental adjustment to chronic stressor

The Mental Adjustment to Cancer (MAC) scale is a self-report questionnaire, validated in a cancer population (Watson et al, 1988), and specifically designed to measure a predefined set of psychological responses to the diagnosis of cancer - a fighting spirit, denial, stoic acceptance and helplessness/ hopelessness.

For this study, the MAC scale was adapted (see Appendix S) to determine the extent to which the subject's mental adjustment to a recent 'natural' stressor was characterised by a *fighting spirit* (the tendency to respond to life stressors in a positive and optimistic manner) and/or *helplessness/hopelessness* (the tendency to become engulfed by the difficulty, to be wholly pessimistic), and whether either contrasting mode of response is associated with the extent of gastric motility disturbance in patients with at least one functional dyspepsia syndrome. The psychometric properties of the altered scale are uncertain.

‘Fighting spirit’ is the only predictor variable used in this study (and only in Study 3) to represent a hardiness/resilience factor. ‘Helpless/hopelessness’ was chosen as a contrasting vulnerability factor. Inclusion of these particular dimensions represents an attempt to include a positive healthy response as well as pathological responses. All participants in the gastric emptying study completed the self-report scale. All had been exposed to at least one chronic difficulty.

#### 2.4.3 DEMOGRAPHIC QUESTIONNAIRE

A brief self-report questionnaire (Appendix T) provided raw data of relevance to the background of the patient population. Questions assessed age and gender, marital and occupational status, personal psychiatric history and its nature, also socioeconomic indicators such as the highest level of occupational and educational attainment. These data contributed to the global description of the patient population, summarised earlier in ‘Subject Characteristics’ (section 2.1.4) and in Tables 3 and 4.

## 2.5 STATISTICAL ANALYSIS

In all studies, the effects of gender and age on symptom and physiological outcomes were taken into account. Several methods were used: only women were included in patient and control groups (Study 5); gender (and age) were included as covariates in the regression analysis; or they were included in subsets of variables as potential predictors. Other potential confounders, particularly of long-term / time-lagged outcomes (Study 2), included baseline symptomatology and baseline levels of emotional distress ie anxiety and depression. The simultaneous control of these variables together with age and gender was important to assessments of the strength of the effects of life stress on subsequent symptom intensity *over and above* these influences. Adjustments for potential confounders (including age and gender) are reported in the text.

As the outcome measures varied across studies, statistical analyses are of necessity reported separately.

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

Univariate and multivariate analyses were performed to determine the relation of the psychological, social and extraintestinal factors to type and number of FGID. Two-tailed Pearson correlation analysis tested the linearity and strength of relations (Bland, 1995): a) between psychological, social and demographic factors and type and number of FGID; b) between extraintestinal symptoms / behaviours and type and number of FGID; and c) between pairs of multisystem variables - number of

FGID, number of extraintestinal symptoms, anxiety and chronic threat. Significant values from multiple hypothesis tests were interpreted according to the method of Hochberg and Benjamini (1990) (Appendix U), a more powerful modification of the Bonferroni procedure.

Logistic regression using the forward-stepwise model selection approach was used to determine the significant factors related to each of the FGID syndromes; this method ensured that the selection of primary features for each syndrome was based on conditional probabilities, while each analysis simultaneously adjusted for the presence of other syndromes (Tabachnick & Fidell, 1983). Linear regression analysis was used when the dependent variable was continuous (number of FGID). At each step of the forward-stepwise procedure, the most significant of the independent variables was entered first (criteria for entry was  $p < 0.05$ ). Each variable was retained in the final model only if significance remained at  $p < 0.05$  (Tabachnick & Fidell, 1983), ie all variables in the predictor models / regression equations reported in this study contribute significantly ( $p < 0.05$ ) to the outcome. Independent variables included demographic, psychosocial, and extraintestinal factors; gender was included in most analyses as an independent variable. Covariates, which included other FGID syndromes, symptom intensity, constancy, and duration, emotional distress, and demographic variables, were introduced appropriately into the analyses.

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

Group patterns of change over time: From symptom intensity and life stress total chronic threat and total goal-frustration measures (assessed at entry, 6mo and

16mo), group *means* and *standard deviations* were calculated. *Within-Subject change over time:* To assess the *covariance* of life stress and symptom intensity over time, global repeated measures of analyses of variance were performed. In one, the changes in symptom intensity scores over time were tested; in the second, these changes were assessed with life stress scores as covariates. The extent to which changes in life stress accounted for changes in symptom intensity scores, was assessed by considering the significance and the magnitude of the changes in symptom intensity with and without the life stress covariates (using the  $\text{Time}_{\text{ws}}$  Effect-size measure, omega squared ( $\Omega^2$ )) (Vaughn & Corballis, 1969).

To determine the *time-lagged* relation of life stress (and emotional distress) to subsequent symptom intensity, and to identify potential mediators of the life stress-symptom intensity relation, linear regression analysis and/or analysis of variance were variously performed (with or without relevant covariates), while logistic regression analysis was used to determine the life stress predictors of improvement versus lack of improvement in symptom intensity over the whole follow-up period. Analyses controlled for the effects of baseline symptom intensity and the duration of symptom intensity at that level prior to entry (Depue & Monroe, 1986; McFarlane et al, 1983); other covariates (demographic, emotional distress and personality) were included when relevant because of their potential to confound with measures of life stress and symptom intensity, and their association over time. To compare the effects of each independent variable on symptom intensity outcome after removal of the confounding effects of all variables in the model, partial correlation values (partial  $\text{Eta}^2$ ) were calculated (Tabachnick & Fidell, 1983).

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

Univariate and multivariate analyses were performed to determine the relation of the psychological factors to each of the gastric emptying parameters. A normalising transformation ( $\log_{10}$ ) was necessary on the latter (Miller, 1990). The relation of individual psychological factors to gastric emptying parameters was assessed by simple linear regression. Unpaired t-tests were performed to determine any sex differences with respect to gastric emptying. Exhaustive search (Jian et al, 1985) among regression models was performed to identify combinations of psychological factors which had independent, statistically significant effects on gastric emptying parameters. In the interests of detecting possible associations between multiple psychosocial variables and gastric emptying outcomes, the statistical significance level was set at  $p < 0.05$ , and marginally significant associations were interpreted with caution.

The direction of the relation between psychological predictors and alterations in gastric emptying are uniformly reported in the text and in the tables in the direction of prolonged half and delay times and slower rates of emptying.

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

Patients were subdivided into three groups according to the presence or absence of delayed transit in each region (stomach, small intestine, colon): a) those with delay in one region (DT1, n=46), b) those with delay in two or more regions (DT2, n=32), or c) those in whom all regions displayed normal transit (NT, n=17). Fifteen patients with accelerated transit were excluded because they had accelerated

transit coexisting with delayed or normal transit. The normal range was established from scintigraphic data obtained in fifty eight healthy asymptomatic subjects. The gender composition of both patient and control groups were similar. For each region, abnormality was defined as one or more scintigraphic parameters outside the 5<sup>th</sup> to 95<sup>th</sup> centiles of the control data for each gender with respect to delay and with respect to acceleration in transit. The accuracy and reproducibility of the scintigraphic method has been documented recently (Kong et al, 1998; Lartigue et al, 1994).

Age and gender distributions in transit subgroups were compared by analysis of variance for age, and the chi-squared test for gender. Analysis of variance was also used to assess differences with respect to scores on the hypochondriasis and depression scales. Stepwise multiple logistic regression analyses were performed to determine the psychological and demographic features (and in separate analyses, the FGID subgroup features) of the DT1 and DT2 subgroups, in contrast to patients with NT, and in comparison with each other. FGID predictor variables included: type of syndrome, combinations of FD syndromes with IBS and FC, and total number of syndromes present. All probability values were two-tailed with alpha set at 0.05.

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

Because of the cyclical nature of fasting small bowel motility, prolonged manometric studies produce repeated measurements of motor parameters with individual subjects. To account for non-independence between repeated measures, the following statistical method was used (Evans et al, 1996). The data were firstly normalised by log transformation and then a generalized linear model technique was used to adjust for repeated measures whereby the correct error term was determined

for subsequent analysis. For a given parameter, repeated measurements were plotted consecutively along the x axis with the quantitative value on the y axis. For an individual subject, a single slope and intercept was then derived and as such was a summary of the repeated measures. Such values were then compared between the groups. If a difference was present, intercepts and slopes were then compared between groups using Student's t test. The association between perception and pain threshold, in controls and patients was assessed also by a generalized linear model technique. For the phase 2 qualitative parameters (other than clustered contractions), because the most frequent observation of these events was zero, the number of events in the study period was divided by the total duration of phase 2 activity in that period, giving an "average" frequency of events (number per hour). Similarly, the total number of phase 3 abnormalities was divided by the total number of MMC cycles. Subject characteristics, character and location of perceived sensation, and motor parameters involving single measurements from each subject, were compared using the Mann-Whitney U test. In patients, rates of small bowel motor abnormality for phase 2, phase 3, and postprandial patterns were compared using the Chi square or Fisher's Exact test. For this purpose patients were classified as having abnormal fasting small bowel motor activity (abnormal phase 2 or phase 3 of the MMC) and/or abnormal postprandial small bowel motor activity, if any parameter relevant to that phase was outside of the normal range for that parameter. The normal range for our laboratory was established from the absolute range of values for each parameter of small bowel motor activity obtained in the nine healthy subjects plus an additional 16 healthy asymptomatic subjects who were studied in the Gastrointestinal Investigation Unit under precisely the same experimental conditions but who did not undergo jejunal distension. In the case of the quantitative fasting parameters and fasting

clustered contractions, a single estimate for each subject was derived by taking the median value of those for all the MMC cycles in the study period. Where necessary, significant values from multiple hypothesis tests were interpreted according to the method of Hochberg and Benjamini (1990) (Appendix U).

For the psychological measures, the significance of mean differences according to normal and heightened perception and pain threshold and normal and abnormal postprandial motor activity, were determined using unpaired t tests; in the interests of detecting possible associations among multiple correlated comparisons alpha was set at 0.05 and marginally significant associations were interpreted with caution. To identify which combination of psychosocial (including demographic) and clinical factors were most powerful in determining normal or heightened sensitivity and normal or abnormal motor activity, logistic regression analyses using forward stepwise procedures were performed. The scales assessing levels of current anxiety (state anxiety) and illness-related attitudes and behaviours (hypochondriasis) enabled a statistical evaluation of the potential confounding effects of anxieties present at the time of jejunal sensitivity assessment.