

# The role of psychological and biological factors in postinfective gut dysfunction

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## Abstract

**Background**—Both psychological and physiological disturbances have been implicated in the aetiopathogenesis of irritable bowel syndrome (IBS).

**Aims**—To investigate how the psychological factors act, and the involvement of infective and physiological factors.

**Methods**—Consecutive patients hospitalised for gastroenteritis reported life events for the previous 12 months, and past illness experiences on standardised questionnaires. They also completed psychometric questionnaires for anxiety, neuroticism, somatisation, and hypochondriasis. In some patients, rectal biopsy specimens were obtained during the acute illness and at three months postinfection.

**Results**—Ninety four patients completed all questionnaires: 22 patients were diagnosed with IBS after their gastroenteritis (IBS+), and 72 patients returned to normal bowel habits (IBS-). IBS+ patients reported more life events and had higher hypochondriasis scores than IBS- patients. The predictive value of the life event and hypochondriasis measures was highly significant and independent of anxiety, neuroticism, and somatisation scores, which were also elevated in IBS+ patients. Rectal biopsy specimens from 29 patients showed a chronic inflammatory response in both IBS+ and IBS- patients. Three months later, specimens from IBS+ patients continued to show increased chronic inflammatory cell counts but those from IBS- patients had returned to normal levels. IBS+ and IBS- patients exhibited rectal hypersensitivity and hyper-reactivity and rapid colonic transit compared with normal controls, but there were no significant differences between IBS+ and IBS- patients for these physiological measurements.

**Conclusion**—Psychological factors most clearly predict the development of IBS symptoms after gastroenteritis but biological mechanisms also contribute towards the expression of symptoms.

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cal mechanism and others supporting a psychological aetiology. Physiological studies have shown differences in intestinal transit as well as contractile and myoelectrical activity, between IBS patients and controls.<sup>2-6</sup> Furthermore, distension of the bowel gives rise to sensations of desire to defaecate and pain at lower distending volumes compared with normal controls.<sup>7-10</sup> However, these studies fail to show convincingly any association between physiological disturbances and the experience of symptoms. Psychological observations have shown that psychological symptoms of anxiety and depression are more common in IBS patients than in either healthy volunteers<sup>11</sup> or patients with organic gastrointestinal diseases,<sup>12</sup> and that stressful life events often precede the onset of chronic bowel symptoms.<sup>13 14</sup> However, studies conducted in the community have concluded that people with IBS symptoms who do not seek medical attention, do not exhibit psychopathology.<sup>15 16</sup> This has led to the suggestion that psychological factors influence illness behaviour rather than the disease itself.<sup>17 18</sup>

All of the observations cited above were conducted after IBS had been present for some time, and while they indicate association, they cannot be said to establish causation. In a recent prospective study, we confirmed that IBS can develop in previously asymptomatic individuals after an episode of acute gastroenteritis.<sup>1</sup> The design of this study allowed us to assess psychometric indexes during recovery from the acute illness and before the development of chronic symptoms and showed that even after controlling for the possible confounding effects of the acute illness, there was a highly significant association between high anxiety, depression, and somatisation scores and the subsequent development of IBS. The results of our earlier study therefore support an important predictive role for psychological factors in the development of IBS symptoms. The present study has extended the remit of our previous study in an attempt to throw some light on how psychological factors might combine with biological changes to bring about symptoms of IBS. In a much larger cohort of patients, we included life event and illness behaviour assessments in our psychological evaluations, and, in a sample of patients, we performed rectal biopsies and physiological assessments.

**Abbreviations used in this paper:** IBS, irritable bowel syndrome; NC, normal controls; WIH, Whiteley Index of Hypochondriasis; WGTT, whole gut transit time; CI, confidence interval; IQR, interquartile range.

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The aetiopathogenesis of irritable bowel syndrome (IBS) remains a controversial topic, with some investigators favouring a physiologi-

Table 1 Demographic characteristics

|                                     | IBS+ (n=22) | IBS- (n=72) | p Value |
|-------------------------------------|-------------|-------------|---------|
| Mean (SD) age, years                | 37.8 (15.8) | 41.1 (16.7) | 0.43    |
| No of female patients (%)           | 14 (64)     | 30 (42)     | 0.12    |
| No of married patients (%)          | 13 (59)     | 40 (56)     | 0.96    |
| No of employed patients (%)         | 17 (77)     | 43 (60)     | 0.21    |
| No with stool organism isolated (%) |             |             |         |
| Salmonella, campylobacter, shigella | 12 (55)     | 39 (54)     | 0.88    |
| Others                              | 3 (14)      | 8 (11)      |         |
| Negative                            | 7 (32)      | 25 (35)     |         |

IBS+, patients who developed IBS postinfection; IBS-, patients who returned to normal bowel habit postinfection.

## Methods

### PROTOCOL

All patients aged 18–80 years who were admitted to the regional department of infectious diseases with a diagnosis of acute gastroenteritis were considered for interview. As this was a prospective study of the development of IBS symptoms, we sought to exclude patients who had symptoms of IBS prior to the onset of acute gastroenteritis. Therefore, patients were excluded if they had a history of any chronic bowel disorder or if they were taking medications likely to affect bowel function. In addition, the usual bowel habits of the remaining individuals were assessed using a validated bowel symptom questionnaire<sup>19</sup> that incorporates questions which identify IBS using the Rome criteria.<sup>20</sup> As a result of this screening process, we excluded 45 patients who had a pre-illness diagnosis of irritable bowel syndrome, 12 patients who had had bowel surgery (for example, colectomy, ileostomy, gastrectomy), and 10 patients who were known to have inflammatory bowel disease. A further 22 patients who did not give a history of bowel complaints were excluded because they were found to have Rome criteria for IBS on their responses to the bowel symptom questionnaire.

Information concerning their acute symptoms and their past medical history was recorded from eligible patients in a standardised manner. They were also asked to complete a series of psychometric questionnaires. A sigmoidoscopy and rectal biopsy were performed at this stage if the patient consented.

Three months after their discharge from hospital, all patients were encouraged to return to clinic to assess their recovery from acute gastroenteritis. If the patient consented, a sigmoidoscopy with rectal biopsy was also done at this time irrespective of their symptom status. In addition, patients who had persistent symptoms were investigated to rule out organic disease if this was clinically indicated. At three months all patients were also asked to complete the bowel symptom questionnaire again. The results of this together with the clinical assessment were used to classify patients into those who had developed IBS symptoms (IBS+) and those who had returned to a normal bowel habit (IBS-). Regardless of their symptom status, all patients were then invited to undergo a series of physiological studies.

### SUBJECTS

#### Patients with acute gastroenteritis

Of the 139 patients who were eligible, 30 declined participation, giving a response rate of

78%. Subsequently, at three months, 15 patients withdrew from the study as they had returned to their normal bowel habits, and were not interested in further participation. The profile of patients who either declined or did not complete the study was similar in terms of age and sex to the group of patients who completed the study, except that a positive stool culture was obtained in only 37% of the former group compared with 62% in the latter.

Of the 94 patients who completed the study, 22 patients (23%) were deemed to have developed IBS based on the bowel symptom questionnaire and clinical assessment; they form the postinfection IBS group (IBS+). They all complained of recurrent abdominal pain associated with a change in bowel habit of which 18 had diarrhoea, two had constipation, and two had an alternating bowel habit. While the majority of IBS+ patients fulfilled the Rome criteria,<sup>20</sup> three patients (two men, one woman) who gave clear histories of recurrent attacks of acute diarrhoea associated with abdominal pain related to bowel movements, failed to meet the Rome criteria because they did not judge the frequency of their diarrhoea to be present for at least 25% of the time. Twelve patients have been followed up for over 12 months and nine of them remain symptomatic.

Of the patients who recovered normal bowel function after their acute illness, 72 completed their three month questionnaires, and they form the postinfection non-IBS control group (IBS-). Table 1 details the demographic characteristics of IBS+ and IBS- patients. Both groups were closely matched for age and marital and employment states, but there was a predominance of women in the IBS+ group. The proportions of patients with no identifiable organisms were also similar in both groups, while the majority had either salmonella, campylobacter, or shigella infections.

### Normal controls

Normal uninfected controls (NC) for the rectal biopsy and physiological studies were drawn from 21 healthy volunteers recruited through advertisements placed in the local hospitals and the university. These subjects did not have criteria for IBS on the bowel symptom questionnaire and also had not had gastroenteritis in the past two years. Eighteen subjects agreed to rectal biopsy: in this group (see table 5) there were more female subjects in the NC group than either the IBS+ or IBS- groups. For the physiological studies, measurements were taken from appropriately matched subjects as described in the next section.

### PSYCHOLOGICAL ASSESSMENTS

#### Life event inventory

Patients were presented with a comprehensive list of life events based on a previously validated inventory<sup>21</sup>; events were of a varied nature ranging from a minor illness and a holiday to a bereavement and a break up in a relationship. They were asked to check and date those events which they had experienced in the 12 months leading up to their acute illness. The total

number of events recorded formed the life event score. Three months after the gastroenteritis, patients were asked to record events which had occurred since their acute illness. As the reporting of life events can be influenced by a tendency either on the part of the patient or the investigator to seek an explanation for the illness,<sup>22, 23</sup> we used a self report methodology and did not ask our patients to judge the impact of individual life events.

#### *Illness behaviour*

Two aspects of illness behaviour were assessed. Firstly, the patient's attitude to disease was assessed using the Whiteley Index of Hypochondriasis (WIH).<sup>24</sup> Secondly, patients were asked a series of questions (see table 4 for details) to form a profile of past illness experience and consultation behaviour in a manner similar to that used by Whitehead *et al.*<sup>25</sup>

#### *Anxiety, neuroticism, and somatisation*

In addition to the above tests, all patients also completed the Hospital Anxiety and Depression Scale,<sup>26</sup> Eysenck Personality Inventory,<sup>27</sup> and a somatisation checklist.<sup>19</sup>

#### SIGMOIDOSCOPY AND RECTAL BIOPSY

The rectal mucosa was first examined using a rigid sigmoidoscope, and the presence of petechiae, granularity, friability, ulcers, or pus was considered to be macroscopic evidence of colitis.

Rectal biopsy specimens were taken from the posterior wall at 8 cm from the anal verge and fixed in 10% formalin/saline. Sections (3 µm thick) were cut and stained with haematoxylin and eosin. Well orientated sections where complete longitudinal crypt profiles could be identified were selected for morphological study. To minimise sampling artefacts, edge areas, traumatic areas, and lymphoid follicles were excluded from analysis. A single high power field (hpf) was defined as the area situated between the superficial epithelium and muscularis mucosae when viewed through a microscope at ×400 magnification (×10 ocular and ×40 objective). A preliminary cumulative means analysis on four randomly selected slides determined that beyond six fields the precision did not increase by more than 5%. Thereafter for each sample, measurements were taken from six contiguous non-overlapping fields beginning from the top left corner of a section. All slides were coded and reviewed by a single, blinded, observer.

#### *Acute inflammatory changes*

The presence of crypt abscesses, cryptitis, or polymorphonuclear cells in any field was taken to indicate acute inflammatory changes in a sample.

#### *Chronic inflammation*

A systematic count was made of all mononuclear cells in six high power fields as defined above. The mean number of mononuclear cells per hpf was used as a measure of chronic inflammation.

#### PHYSIOLOGICAL ASSESSMENTS

These tests were done between three and six months postinfection.

#### *Measurement of whole gut transit time*

Whole gut transit time (WGTT) was measured using radio-opaque markers and collection of a single stool sample following the method developed by Cummings and Wiggins.<sup>28</sup> Measurements were taken from 18 patients in the IBS+ group, and age and sex matched samples were drawn from the IBS- and NC groups as age and sex have been shown to influence transit times.<sup>2</sup>

#### *Rectal distension studies*

Sensory and motor responses to rectal distension were assessed by a method that has been previously described by us,<sup>9</sup> and is similar to that used by other investigators.<sup>29</sup> Essentially, the rectum was distended by means of an intrarectal balloon inflated with progressively increasing volumes of air in an intermittent phasic manner while intrarectal pressure was continuously monitored by a water perfused pressure transducer system. From this study, the lowest balloon volumes required to induce sensations of wind, desire to defaecate, urgency of defecation and discomfort, and manometrically defined repetitive rectal contractions, as well as rectal compliance were derived as previously described.<sup>9</sup> Measurements were taken from 11 female and five male patients in the IBS+ group. Sex matched samples were drawn from the IBS- and NC groups, as gender differences in rectal sensitivity were reported in a previous study.<sup>30</sup>

#### STATISTICAL ANALYSIS

Sample sizes were based on preliminary studies from our centre.<sup>1, 31, 32</sup> Residual plots of all data sets were examined to decide whether parametric or non-parametric procedures were appropriate. Summary statistics of normally distributed data are expressed as means and standard deviations (SD) while those of non-parametric data sets are expressed as medians with interquartile ranges (IQR). Analysis of variance was performed in the first instance if more than two groups were compared. The 95% confidence interval (CI) for the mean difference between groups was calculated using bootstrap methods which work by resampling from the observed data and thus make no distributional assumptions.<sup>33</sup> Categorical data were analysed using the  $\chi^2$  test with continuity correction or Fisher's exact test as appropriate. Forward stepwise logistic regression analysis was used to identify predictive factors and to control for confounding factors including age, sex, marital status, employment status, and stool culture status.

#### Results

##### PSYCHOLOGICAL DETERMINANTS

As in our previous report,<sup>1</sup> anxiety and neurotic scores taken at the time of the initial illness were higher in IBS+ than in IBS- patients (table 2). In addition, the present study found that life event and hypochondriasis scores were

Table 2 Psychometric scores

|  | IBS+ (n=22)<br>Mean (SD)<br>Median (IQR) | IBS- (n=72)<br>Mean (SD)<br>Median (IQR) | Mean difference<br>(95% CI) | p Value |
|--|--|--|-----------------------------|---------|
| Anxiety score                              | 8.3 (4.6)<br>7.5 (4.0–12.5)              | 5.7 (3.4)<br>5.0 (3.0–9.0)               | 2.6 (0.5–4.5)               | 0.01    |
| Somatisation score                         | 3.1 (2.5)<br>3.0 (1.0–4.3)               | 1.5 (1.6)<br>1.0 (0.0–2.8)               | 1.6 (0.6–2.7)               | 0.003   |
| Neuroticism score                          | 11.7 (4.7)<br>10.5 (8.8–15.3)            | 8.4 (4.9)<br>7.5 (4.0–12.0)              | 3.4 (1.2–5.6)               | 0.008   |
| Life event score 1 year<br>before illness  | 4.6 (3.3)<br>4.0 (2.0–7.0)               | 2.4 (1.9)<br>2.0 (1.0–3.8)               | 2.3 (0.9–3.7)               | 0.001   |
| Life event score 3<br>months after illness | 2.0 (2.2)<br>1.0 (1.0–2.0)               | 0.7 (0.9)<br>0.0 (0.0–1.0)               | 1.29 (0.4–2.2)              | 0.001   |
| Hypochondriasis score                      | 3.1 (2.5)<br>3.0 (0.8–6.0)               | 1.7 (1.8)<br>1.0 (0.0–2.8)               | 1.4 (0.3–2.5)               | 0.02    |

IQR, interquartile range; CI, confidence interval.

Table 3 Multivariate analysis of demographic, stool, and psychological variables as predictors for development of postinfectious IBS

| Variables         | Relative risk | Corrected RR (95% CI) | Significance |
|-------------------|---------------|-----------------------|--------------|
| Life events       | 1.95          | 1.97 (1.72–2.35)      | 0.001        |
| Hypochondriasis   | 2.27          | 2.04 (1.75–2.49)      | 0.008        |
| Somatisation      | 2.38          | –                     | –            |
| Neuroticism       | 2.49          | –                     | –            |
| Anxiety           | 2.72          | –                     | –            |
| Age               | 2.68          | –                     | –            |
| Sex               | 62.55         | –                     | –            |
| Marital status    | 4.15          | –                     | –            |
| Employment status | 251.41        | –                     | –            |
| Stool status      | 2.69          | –                     | –            |

RR, relative risk; CI, confidence interval.

significantly greater in IBS+ than in IBS- patients. Forward stepwise logistic regression analysis was performed to control for possible confounding factors and to test for an interaction among the psychological variables. The results (table 3) showed that age, sex, marital and employment states, and whether the stool culture was positive or negative, did not influence the predictive effect of life event and hypochondriasis scores which were the only psychological variables that remained independent and highly significant risk factors for the development of IBS in this model.

The life event score was the total number of recorded life events in the one year preceding gastroenteritis. When the different categories of life events were examined, more IBS+ than IBS- patients had experienced an event that involved some disruption of personal relationships (71% versus 29%; p=0.005). In addition,

Table 4 Illness behaviour profile

|  | IBS+ (n=22) | IBS- (n=72) | p Value |
|--|-------------|-------------|---------|
| Illness experienced in preceding 12 months |             |             |         |
| Two or more colds                          | 13 (59)     | 36 (50)     | 0.12    |
| Visited doctor for cold                    | 3 (14)      | 6 (8)       | 0.43    |
| Two or more acute physical illnesses       | 5 (23)      | 8 (11)      | 0.18    |
| Visited doctor for acute illness           | 5 (23)      | 8 (11)      | 0.18    |
| Visited doctor for non-acute reason        | 7 (32)      | 25 (35)     | 1.0     |
| Hospitalised                               | 1 (5)       | 7 (10)      | 0.68    |
| Missed work more than four days            | 10 (46)     | 16 (22)     | 0.14    |
| Past medical history                       |             |             |         |
| Indigestion                                | 6 (27)      | 17 (24)     | 0.95    |
| Gastroenteritis                            | 4 (18)      | 15 (21)     | 1.0     |
| Asthma                                     | 2 (9)       | 9 (13)      | 1.0     |
| Hay fever                                  | 0 (0)       | 19 (27)     | 0.005   |
| Allergy                                    | 3 (14)      | 17 (24)     | 1.0     |
| Rash                                       | 3 (14)      | 15 (21)     | 0.55    |
| Hypertension                               | 4 (18)      | 9 (13)      | 0.50    |
| Hysterectomy                               | 3 (14)      | 5 (7)       | 0.58    |
| Cholecystectomy                            | 0 (0)       | 2 (3)       | 1.0     |
| Appendectomy                               | 2 (9)       | 10 (14)     | 0.73    |
| Non-abdominal surgery                      | 9 (41)      | 25 (35)     | 0.78    |

Results expressed as no (%) of patients in the group who had a positive response.

compared with IBS- patients, IBS+ patients also experienced an excess of life events in the three months following gastroenteritis (see table 2). Although IBS+ patients had higher hypochondriasis scores than IBS- patients, when the three subscales of the WIH were analysed, IBS+ patients scored significantly higher only for bodily preoccupation (IBS+ 1.3 (1.0) versus IBS- 0.7 (0.9); p=0.005), but not for disease phobia and disease conviction.

Table 4 shows the recent illness experience and past medical history of this cohort of patients. Both groups were similar in their recent illness experiences and utilisation of health care resources. With regard to the past medical history, IBS+ and IBS- patients had similar rates for common medical disorders, except that IBS- patients were more likely to suffer with hay fever (p=0.008). There were no significant differences in rates for common abdominal and non-abdominal surgical procedures.

SIGMOIDOSCOPY AND RECTAL BIOPSY

Ten IBS+ and 19 IBS- patients had sequential sigmoidoscopy and rectal biopsies during both the acute illness and postinfective periods (table 5). As the level of inflammation may be dependent on the time interval between onset of gastroenteritis and the time when the biopsy was performed, this time interval was measured but no significant difference was found between the IBS+ and the IBS- patients, and no correlation was found between the interval to biopsy and cell counts (r=-0.041, p=0.832). The proportions of these IBS+ and IBS- patients who had received antibiotics and who had an enteric pathogen isolated in stool samples were also similar.

Acute inflammatory changes

During the acute illness most patients had either normal looking mucosa or only minor changes. Ten patients (three IBS+, seven IBS-) had definite features of colitis on sigmoidoscopy which were confirmed by histology; among these 10 patients, four had salmonella, three had campylobacter, one had shigella, one had *Clostridium difficile* toxin, and one had no organism isolated from stool samples. When all these patients were reexamined after three months their colitic changes had resolved macroscopically and microscopically, and further follow up has excluded ulcerative colitis. Microscopically, acute inflammatory cells were also noted in a number of postinfective samples (20% of IBS+ and 11% of IBS- samples; NS), but none of these constituted features of ulcerative colitis.

Chronic inflammation

During gastroenteritis, rectal biopsy specimens taken from both the IBS+ group (mean 98.4 (SD 17.4); p=0.008) and the IBS- group (mean 99.8 (SD 35.0); p=0.03) showed significantly greater chronic inflammatory cell counts than normal controls (mean 79.1 (SD 16.9)). However, despite similarly increased chronic inflammatory cell counts during gastroenteritis, when biopsy specimens were taken

Table 5 Sigmoidoscopy and rectal biopsy findings

|  | IBS+ (n=10)    | IBS- (n=19)  | Controls (n=18) |
|--|----------------|--------------|-----------------|
| Mean (SD) age, years                                       | 39.2 (19.1)    | 46.8 (16.6)  | 30.1 (10.2)     |
| No of female subjects (%)                                  | 4 (40)†        | 7 (37)†      | 14 (78)         |
| No received antibiotics (%)                                | 8 (80)         | 13 (62)      | –               |
| No of positive stool cultures (%)                          | 6 (60)         | 10 (53)      | –               |
| <i>Acute infection biopsy samples</i>                      |                |              |                 |
| Mean (SD) interval from onset to biopsy, days              | 10.6 (18.6)    | 5.1 (4.6)    | –               |
| No of patients with macroscopic colitis (%)                | 3 (30)         | 7 (37)       | 0 (0)           |
| No of biopsy specimens with acute inflammatory changes (%) | 3 (30)         | 3 (16)       | 0 (0)           |
| Mean (SD) no of chronic inflammatory cells per hpf         | 98.4 (17.4)‡   | 99.8 (35.0)† | 79.1 (16.9)     |
| <i>Postinfection biopsy samples</i>                        |                |              |                 |
| Mean (SD) interval from onset to biopsy, days              | 106.4 (36.2)   | 105.6 (25.9) | –               |
| No of patients with macroscopic colitis (%)                | 0 (0)          | 0 (0)        | 0 (0)           |
| No of biopsy specimens with acute inflammatory changes (%) | 2 (20)         | 2 (11)       | 0 (0)           |
| Mean (SD) no of chronic inflammatory cells per hpf         | 105.7 (23.3)*‡ | 83.2 (29.4)  | 79.1 (16.9)     |

\*p<0.05 versus IBS-; †p<0.05 versus normal controls; ‡p<0.01 versus normal controls.

from these same patients three to six months after gastroenteritis, those from IBS+ patients showed significantly greater counts than those from IBS- patients. In the postinfective biopsy samples taken from IBS+ patients the chronic inflammatory response persisted with a mean cell count of 105.7 (SD 23.2) that was significantly elevated above normal controls (mean 79.1 (SD 16.9); p=0.002) and also above IBS- patients (mean 83.2 (SD 29.4); p=0.046), whereas postinfective samples from IBS- patients showed a decline in chronic inflammatory cell counts to a level that was not significantly different from normal controls.

#### PHYSIOLOGICAL MEASURES

Both IBS+ and IBS- patients had a significantly faster WGTT than normal controls, but values were not significantly different from each other (see table 6). Both groups of patients had significantly lower rectal distension thresholds for desire to defaecate and repetitive rectal contractions, as well as decreased rectal compliance compared with normal controls (see table 7). IBS+ patients also had significantly lower thresholds for urgency and discomfort compared with normal controls. As with the transit studies, there were no statistically significant differences between IBS+ and IBS- patients on any of the rectal parameters.

Table 6 Whole gut transit times (WGTT)

|                           | IBS+ (n=18)        | IBS- (n=18)       | Controls (n=18)  |
|---------------------------|--------------------|-------------------|------------------|
| Mean (SD) age, years      | 42.6 (18.9)        | 36.4(12.4)        | 39.4(9.7)        |
| No of female subjects (%) | 11 (61)            | 11 (61)           | 11 (61)          |
| Median (IQR) WGTT, h      | 34.4 (29.8–40.0)** | 44.8 (31.0–53.5)* | 55.2 (38.6–65.5) |

\*p<0.05, \*\*p<0.01 versus normal controls. There were no significant differences between IBS+ and IBS- patients.

Table 7 Sensory and motor responses to rectal distension

|   | IBS+ (n=16)     | IBS- (n=16)    | Controls (n=16) |
|---|-----------------|----------------|-----------------|
| Mean (SD) age, years                      | 43.4 (18.0)     | 40.3 (15.6)    | 32.1 (9.1)      |
| No of female subjects (%)                 | 11 (69)         | 11 (69)        | 11 (69)         |
| Wind                                      | 30 (10–40)      | 20 (20–40)     | 20 (20–40)      |
| Desire to defaecate                       | 40 (40–60)**    | 50 (40–74)**   | 80 (60–100)     |
| Urgency                                   | 80 (60–95)**    | 80 (80–150)    | 150 (100–200)   |
| Discomfort                                | 125 (80–150)**  | 150 (112–200)  | 200 (150–250)   |
| Repetitive rectal contractions            | 30 (10–40)**    | 40 (20–40)*    | 70 (35–113)     |
| Rectal compliance, ml/cm H <sub>2</sub> O | 2.7 (1.8–3.7)** | 2.9 (1.9–5.0)* | 5.0 (3.1–6.4)   |

Results are presented as the median (interquartile range) threshold volumes of distension (ml of air) required to induce the reported response.

\*p<0.05, \*\*p<0.01 versus normal controls. There were no significant differences between IBS+ and IBS- patients.

## Discussion

The results obtained from this study reinforce and extend the observations of our previous study<sup>1</sup> by showing not only that anxiety, neuroticism, and somatisation predict the development of IBS in patients suffering from acute gastroenteritis, but also that life event and hypochondriasis scores are higher in patients who develop postinfectious IBS. It is of course possible that patients with a neurotic personality and an anxious predisposition might be more likely to recall life events and past illness experiences. However, forward logistic regression analysis for interactions among the different psychological variables indicated that both the life event and hypochondriasis scores were independent of the other psychological symptoms. The prospective design of this study underscores the importance of all of these psychological factors in the development of postinfectious IBS. Furthermore, the fact that the diagnosis of IBS was made on the basis of a post hoc questionnaire rather than doctor's records suggests that the psychological factors do indeed predict the development of symptoms and not just illness behaviour. Further support for this conclusion, is the observation that the two groups of patients did not differ significantly in their reporting of past illness experiences and consultation behaviour. Thus despite a higher reporting of somatic symptoms, and a tendency to perceive physical sensations as symptoms of disease, as suggested by their higher hypochondriasis scores, IBS+ patients had not sought medical consultation and treatment more frequently than their IBS- counterparts. Thus, we suspect that Whitehead and Crowell's<sup>17</sup> and Drossman's<sup>18</sup> claim that psychosocial stress does not so much determine the development of IBS as who goes to the doctor with bowel symptoms is perhaps an oversimplification of a complex concept. The definition of abnormal illness behaviour encompasses not only the ways in which symptoms are perceived and evaluated, but also how they are acted upon.<sup>34</sup> Other studies have indicated how consultation behaviour is also determined by factors other than psychopathology. For example, Jones and Lydeard<sup>35</sup> found that the consultation rate for patients with IBS symptoms was 47% in those with rectal bleeding, whereas in those without bleeding it was

only 25%, and Heaton and colleagues<sup>36</sup> found that IBS patients who consulted a doctor had bowel habits that were more erratic than those who did not consult.

Given the pathogenic role of psychological factors, do inflammatory and physiological mechanisms also play a part, or is it a purely psychological mechanism? Evidence exists to suggest that psychological arousal can produce a heightened awareness of somatic symptoms arising from the gut. Investigators from Barcelona have shown that mental attention focused on the stomach increased the perception of gastric distension.<sup>37</sup> Similarly focus of attention could be provided by the association of a gastrointestinal illness with psychological stress. Thus if the psychological stress is ongoing, the bowel symptoms persist and come to represent the emotional distress.<sup>38</sup>

On the other hand, evidence of rectal inflammation which persisted after gastroenteritis in the IBS+ patients, but which resolved in the IBS- patients, suggests that emotional factors might act to enhance the biological changes through a psychoneuroimmunological axis and could contribute towards the expression of symptoms.<sup>39</sup> Data from animal experiments indicate that stress can have a profound influence on inflammatory events in the gut. For example, mild stress applied to rats prior to the experimental induction of colitis enhanced the inflammatory response,<sup>40</sup> while in rats that had recovered from experimental colitis, mild stress similarly caused reactivation of inflammation.<sup>41</sup> Thus, it is possible that psychological stress could have increased or sustained the inflammatory response to infection, and this might explain the persistence of a chronic inflammation in the IBS+ group that was not observed in the IBS- group.

The observation that the measurements of gut function after gastroenteritis were significantly different from normal controls, irrespective of whether they developed IBS symptoms or not, suggests that these changes developed as a result of gastroenteritis. There is some support for this from a recent study which showed that experimental induction of acute diarrhoea by laxative ingestion could sensitise the rectum in normal volunteers.<sup>42</sup> However, the finding of these physiological changes in the asymptomatic group (IBS-) questions their relation to the experience of IBS symptoms by our IBS+ patients. Perhaps the physiological changes predispose to IBS but psychological factors are required to bring out the perception of these physiological changes as symptoms. Physiological sensitisation of the bowel would offer one explanation as to how postinfectious IBS develops in psychologically predisposed individuals. In other words there has to be some gastrointestinal priming in association with psychological factors for symptoms to develop. It is as if the sensitised gut is recruited to express the patient's emotional distress.<sup>38</sup>

However, it should be acknowledged that IBS is a heterogeneous disorder, and not all patients with IBS give a preceding history of gastroenteritis. Other events that may precede

the onset of IBS include pelvic surgery, the use of antibiotics, and psychological trauma. In many patients, no identifiable trigger can be recognised. Thus, our observations and the model we propose apply specifically to postinfectious IBS. Different mechanisms may apply to different subgroups of IBS.

Nevertheless, our study represents an advance in our understanding of this condition as it allows us to conceptualise this disorder in an interactive manner. For example, a causal pathway where psychological and biological factors are required may explain why not all psychologically disturbed people have IBS,<sup>43</sup> and why not all who have gastroenteritis develop IBS. Furthermore, this psychobiological model could also explain the gastrointestinal expression of the Gulf War syndrome. Soldiers engaged in combat are obviously in a highly stressful environment. The chronic gastrointestinal symptoms of Gulf War veterans are consistent with IBS.<sup>44-45</sup> One case control study suggests that the majority of those affected had an episode of illness consistent with gastroenteritis during their deployment in the Gulf.<sup>44</sup> Another study showed physiological (enhanced rectal sensitivity) and psychological (anxiety and depression) disturbances in these Gulf War veteran patients that were similar to those in IBS patients.<sup>45</sup> Furthermore, at least three studies<sup>44-46-47</sup> have reported mild increases in chronic inflammatory cells in colonic biopsy specimens taken from those afflicted. All these observations resonate with the early observations recorded on postinfectious IBS<sup>48-50</sup> which were based on soldiers and other servicemen who had suffered an episode of enteric infection while fighting in a war.

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