The Hypersensitive Gut: Adequate Approach or Further Confusion?

Key Words
Evoked cerebral potentials
Functional disorders
Gut distension
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Non-cardiac chest pain
Non-ulcer dyspepsia
Rectal motility

The 'IBIS' Club

On December 19th, 1992, a newly constituted club of European experts on the irritable bowel syndrome (IBS) convened to a round table conference about the ‘hypersensitive, hyperreactive gut’. This meeting was the first in a series of meetings which in the future will cover various subjects related to IBS. The discussions consisted of short statements, an extended brainstorming, and finally the attempt to pronounce a ‘state-of-the-art’ opinion. The proceedings are summarized in the following.

The subject ‘hypersensitive, hyperreactive gut’ was chosen as the opening theme because of the recent accumulation of evidence that the key to the symptomatology of IBS patients is to be sought less in objectifiable alterations of the bowel function but in the mental and social processing of individual perception [1]. Therefore, afferent [2] (‘hypersensitive’) as well as efferent [3] (‘hyperreactive’) mechanisms would of interest.

Should the Term Irritable Bowel Syndrome (IBS) Ever Be Used?

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There are valuable arguments to put the definition ‘IBS’ into doubt immediately due to diagnostic overlapping with syndromes such as lactose intolerance, giardiasis, slow transit constipation, non-ulcer dyspepsia, psychiatric disorders, etc. This dilemma has been substantiated in 134 patients who underwent a standardized symptom-oriented investigation, as a result of which only about 50% of the patients stayed with the probable diagnosis of IBS [Müller-Lissner, pers. commun.]. Thus, the question of gut hypersensitivity can only be discussed adequately if patient populations are carefully defined prior to investigation [4]. The same is applicable to clinical intervention and follow-up series of IBS.

In line with a recent international definition of IBS by Thompson et al. [5], a basic symptomatology occurs in patients with IBS, which is given in table 1 [6]. The duration of the syndrome should always be stated (acute, subacute or chronic, defined as lasting >3 or >6 months).
**Table 1.** Symptom criteria for IBS [after Thompson et al., 6]

<table>
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<tr>
<th>Symptom Criteria</th>
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| 1 Abdominal pain or discomfort which is | a Relieved with defecation  
b And/or associated with a change in frequency of stool  
c And/or associated with a change in consistency of stool |
| 2 Two or more of the following, at least a quarter of occasions or days | a Altered stool frequency\(^1\)  
b Altered stool form (lumpy/hard or loose/watery stool)  
c Altered stool passage (straining, urgency, or feeling of incomplete evacuation)  
d Passage of mucus  
e Bloating or feeling of abdominal distension |

\(^1\) For research purposes, 'altered' may be defined as >3 bowel movements/day or <3 bowel movements/week.

For clinical and research purposes it will be useful to define the subtype(s) of IBS, e.g. IBS with spasitic constipation, IBS with changing bowel habits and abdominal distension, and IBS with diarrhea and abdominal pain predominantly [7].

In clinical practice, IBS should probably be regarded as a 'working diagnosis' (similar to 'non-ulcer dyspepsia') recording the 'positive diagnostic criteria', such as the Manning and the Krus indices (table 2) [8, 9] and in particular the investigations performed for the exclusion of symptomatically overlapping organic diseases. For mainly scientific purposes, more or less selected symptomatic subgroups of IBS should be investigated in which patients have documented inclusion and exclusion criteria [4].

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**Table 2.** Manning and Krus indices

- **Criteria of Manning et al. [8]**
  - Visible abdominal distension
  - Pain relief with defecation
  - More frequent stools at pain onset
  - Looser stools at pain onset
  - Mucus per rectum
  - Frequent feeling of incomplete evacuation

- **Criteria of Krus et al. [9]**
  - Presence of a symptom implies adding the corresponding factor\(^1\)
  - Abdominal pain as reason for encountering or flatulence or irregularities of bowel movement +34
  - Duration complaints >2 years +16
  - Pain, burning, cutting, very strong, terrible feeling of pressure, dull, boring, not so bad +23
  - Alternating obstipation and diarrhea +14
  - Abnormal physical findings and/or history pathognomonic for any diagnosis other than IBS −47
  - ESR >20 mm/h −13
  - WBC >10,000 cm\(^3\) −50
  - Hemoglobin male <14 g%, female <12 g% −98
  - History of blood in stool −98

\(^1\) Rule: cutpoint −.44 after adding up.

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**Why Do Some Patients with IBS Consult a Physician?**

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The question arises why some persons with IBS symptoms consult a physician and others do not [10]. The first point to be taken into consideration is related to the epidemiology of IBS: several questionnaire-based surveys conducted during the last decade have shown a prevalence of IBS-like symptoms in the general population ranging from 5 to 20% [11-15]. The only available study conducted with a different methodology (direct interview and/or physician records) gives a much lower prevalence (1.6–2.9%) [11], but this figure is almost certainly an underrepresentation of the phenomenon.

From the various available studies the health care seeking pattern of the population with IBS symptoms appears to be predictable: as many as 40–50% of subjects emerge as patients during the following year, whereas a considerably lower number is nowadays admitted to hospital for clinical evaluation and therapy [11]. The reasons leading to consultation are probably multiple, interacting with each other, and probably mostly of a nonmedical nature [14, 15]. For example, it has been reported that whereas in the Western World mainly women consult a physician for their symptoms, in India men predominate due to the sociocultural characteristics of that society.

Among the medical reasons, there is a higher prevalence of intestinal symptoms in consultants than in non-consultors or controls [14]. Pain is the most frequent intestinal symptom which leads the patient to consult a
doctor, both in men and in women, the second being the presence of mucus in the stool in men, and loose stools with pain in women [14]. The number of symptoms present in individual patients has been shown to be directly related to the likelihood of doctor consultation; for example, only 16% of men with one IBS symptom consult a physician, as compared to 75% of those with more than five symptoms [14]. Interestingly, IBS consulters show a peculiar behavior in that they focus on symptoms and perceive them as serious enough to require medical attention. Accordingly, they complain of gastrointestinal and non-gastrointestinal symptoms in a higher percentage than nonconsulters or controls, and have a higher number of visits to the doctor.

Separating IBS consulters on the one hand from IBS nonconsulters and controls on the other, it seems that personality deviations are more frequent in the former than in the latter group [15, 16]. Concerning perception of life events, IBS consulters report less positive as well as less negative stress occasions, a constellation known to be compatible with a depressive personality trait.

Thus, factors converting a person from an IBS nonconsultor to an IBS consultor are mainly of a sociocultural and psychological nature. However, the role of gut hypersensitivity in this context has not been sufficiently investigated.

Is There a Lowered Visceral Pain Threshold in the IBS, Non-Ulcer Dyspepsia, and Non-Cardiac Chest Pain?

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Ritchie [17] was the first to show that patients with symptoms of IBS tolerated smaller volumes of balloons inflated in their rectum than controls. Similar investigations have been performed recently and have, with a few exceptions, indicated that IBS patients have a higher sensitivity or pain perception in their large and small intestine than healthy controls [18–20].

These findings were observed despite the varying nature of the diagnostic criteria for IBS and the variety of control populations. Some studies, using the ice-water immersion test, indicate that IBS patients do not have a generally lowered pain threshold [21]. Thus, in IBS, the difference in pain perception may be confined to the visceral area. However, attention has to be given to the fact that IBS patients and also controls who subject themselves to motility and pain studies may represent a selected sample, and that conclusions drawn from such experiments may not be extendable to the 'every-day' IBS patient seen by a general practitioner.

Under the hypothesis that functional gastrointestinal disorders may have a common neurophysiological denominator, distension studies were also performed in patients with 'non-ulcer dyspepsia' by a few groups of investigators. They showed that differences in perception of discomfort between patients and controls were similar to those found in IBS [22, 23].

A third group of functional disorders in which a decreased visceral pain threshold was found is the 'non-cardiac chest pain' syndrome (NCCP). The most recent findings reported by Smout et al. [24] concerned the so-called 'evoked cerebral potentials', observed after distension of balloons in the esophagus of patients with NCCP. The investigations showed that patients with NCCP needed lower distension volumes than controls to elicit similar pain sensations and amplitudes of the evoked potentials. In further studies, the subjective and central nervous phenomena could be suppressed by applying local anesthesia to the esophageal mucosa prior to the distension experiments. The authors therefore concluded that the increased sensitivity in non-cardiac chest pain originates from hypersensitive receptors in the esophagus, rather than from a different central-nervous handling of the information transmitted centripetally [25].

The evoked-potential technique may give access to further research concerning the gut-brain axis, including psychological and other personality-bound factors, in patients with functional gut disorders.

The Role of Gut Distension in IBS: Can It Be Tested?

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The feeling of distension and so-called 'visible distension' belong to the Manning criteria [8] and are reported by two-thirds of IBS patients. Abdominal pain is the other important symptom. The question arises as to the correlation of both symptoms. The correlation was already reported by Ritchie [17] and was well documented experimentally by Swarbrick et al. [26] who investigated pain
localisation following balloon distension at various sites of the colonic framework. Swarbrick and co-workers found a clear difference in pain experience between controls and IBS patients. In the latter, pain was experienced predominantly in the left and lower abdomen, also following distension at distant bowel sites. The pathophysiology of the distension-evoked pain remains unclear. Some authors described an altered recto-sigmoid motility pattern simultaneous with the pain sensation [17] and others did not [27, 28]. Alternative explanations could be a decreased volume compliance, which has been suggested by Chevalier et al. [29], or, as described above, a decreased tolerance/lowered threshold for an identical distension in patients as compared to controls.

Testing the increased sensitivity for bowel distension as a diagnostic criterion for IBS is far from clinical reality. Direct testing in the left colon is possible and is probably not more cumbersome for patients and physicians than other diagnostic procedures in IBS. Colonoscopy may add some important clues concerning hypersensitivity [20]. However, the sensitivity and specificity of these methods has to be confirmed in both unselected and symptomatically selected IBS patients.

Alternatively, electromyographic or motility patterns closely connected with painful distension should be identified and further investigated with regard to their positive and negative predictive value for IBS and its subforms. Several authors demonstrated that the measurement of 'long spike bursts' (LSB), using an EMG registration, could be a candidate test for this purpose [30, 31].

However, it has to be admitted that motility patterns are far from homogeneity in various subforms of IBS, in particular when tested with ambulatory 24-hour measurements [32]. Testing will probably always remain the domain of specialized laboratories.

**Is the Irritable Bowel Really Irritable (with Special Reference to the Possible Effect of Intraluminal Stimuli Including Distension, Short-Chain Fatty Acids, and Bile Acids)?**

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A number of possible stimuli or noxes could elicit a sensation of pain and/or discomfort in the hypersensitive/hyperreactive gut: certain foods [33]; drugs; medical investigations [20]; but also physiological events such as bowel distension, intrinsic motor activity of the bowel [18], and cholecystokinin. Little is known about the effects of intraluminal bile acids (BAs) and short-chain fatty acids (SCFAs). The former are absorbed by the colonic mucosa and, in experiments, influence the permeability of colonic smooth muscle cells, promote opening of calcium channels, and block cholinesterase activity; the latter – fermentation products of unabsorbed dietary fibre – may stimulate motor activity by influencing the sensory and cholinergic nerves.

In own experiments, involving 9 female patients with constipation-dominant IBS and 5 male controls, the effect of intracolonic stimulation by distension and 'physiological' concentrations of deoxycholic acid and of SCFAs was tested. In a protracted experiment, the stimuli were applied in random order via colonoscopically placed catheters reaching to the splenic flexure, and were interrupted by periods of infusion of control solutions.

Outcome parameters were the subjective sensations of patients or volunteers as well as measurable motor activity. The IBS patients tolerated distension much less than the controls: pain was provoked by a balloon mean volume of 75 ml as compared to 171 ml in controls.

The pain experienced by the patients was similar to their 'familiar' pain in contrast to the pain experience of the volunteers. BAs provoked pain in nearly all patients but none of the volunteers, and so did SCFAs. However, whereas the pain experience following bile acids was paralleled by increased motor activity of the left colon, this was not the case during the pain sensations provoked by SCFAs. Two different types of motor activity observed in this context were repetitive propulsive activity and increased irregular activity.

It was concluded from these original experiments that the IBS patients investigated seemed to have nonspecific irritability of the colon for the most varying stimuli, and that the symptoms of the patients were not necessarily related to altered motor activity.

**Desensitization of the Irritable Gut by Hypnosis?**

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In a study published in 1984, 15 IBS patients were treated with repeated sessions of hypnosis lasting 30–45 min, whereas a control group received placebo tablets.
and minor psychotherapy. After 3 months of treatment, the hypnosis-treated group fared much better than the controls [34]. By now, in Manchester, several hundred patients have been treated by a number of hypnoti-
pists, presently in much shorter sessions. The success rate is still about 80% in the long term, which must be regarded as a high figure as seen by the intractability of most patients by previous therapy [35]. Some patients need 'boost' sessions once a year.

Following the initial success of hypnotherapy, inves-
tigations were done to the 'mode of action', i.e. the physio-
logical effects of hypnosis in IBS. Obviously, the effect is not predominantly of a psychological nature as patients with personality disturbances respond less than others. Controlled follow-up experiments show that hypnosis lowers the sensitivity of the distal colon in those cases where sensitivity is increased [36]. In the responding patients hyposensitization could be recorded within as well as outside the state of hypnosis.

So far it is unknown by which pathways hypnosis influences the hypersensitivity of the gut: modulation of the sensory input is one option, but the field is obviously open for further research.

Conclusions

The concept of the 'hypersensitive, hyperreactive gut' forms a unifying hypothesis in the pathophysiology of IBS and is now widely accepted. The 'hypersensitive, hyper-
reactive gut' probably has close affinities to other 'func-
tional' gastrointestinal disorders such as non-cardiac chest pain and non-ulcer dyspepsia. Further research into the effenter and afferent pathways of the 'gut-brain axis' may not only become helpful in diagnosing and treating patients with IBS, but could also contribute to a deeper understanding of so-called 'psychosomatic' disorders in general.

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