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Labor für Klinische Psychophysiologie
Nr. 29

FORSCHUNGSBERICHTE

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OTTO - SELZ - INSTITUT

FÜR

PSYCHOLOGIE UND ERZIEHUNGSWISSENSCHAFT

DER

UNIVERSITÄT MANNHEIM (WH)

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In Vorbereitung zur Publikation in Journal of Gastrointestinal Motility

Diese Arbeit wurde von der Deutschen Forschungsgemeinschaft unterstützt
(Ho 904/3-1 ff.)

Forschungsberichte aus dem Otto-Selz-Institut für Psychologie und Erziehungswissenschaften der Universität Mannheim
ISSN 0931-1394

ABSTRACT

Visceral hypersensitivity as shown in lowered pain threshold to distension of the colon in IBS patients could explain a major part of the clinical symptomatology. Due to insufficient subgroup specifications, confoundation of visceral transduction with sensitivity, elicited responses, and non-sensory pain components, earlier studies have not been conclusive. The present study uses test procedures, which allow isolation of these components. It compared sensation and motility responses to graded distension of three IBS subgroups (diarrhea-predominant, constipation-predominant, alternating; N = 46) with healthy controls (N = 14) selected from large community samples according to strict criteria. Results replicated earlier findings of reduced volume thresholds of IBS patients with abdominal pain symptoms and diarrhea, but not in constipated patients who did not differ from controls. Lowered colonic compliance was sufficient to explain visceral hypersensitivity as well as correlated increases in elicited contractions. Increased pressure thresholds showed that these patients do not suffer from genuine hyperalgesia, but from abnormal tonic reflex response producing steeper pressure-volume curves. Thresholds for non-nociceptive sensations showed the same pattern. No differences in somatic pain sensitivity were found between groups. Analysis of these findings show that reliable visceral pain tests are important for the differentiation of IBS subgroups and other syndromes with gastrointestinal pain.

KEY WORDS: IBS, visceral hyperalgesia, visceral pain, visceral perception, compliance, symptom specificity.

INTRODUCTION

Increased visceral pain sensitivity has been reported repeatedly to be associated with the irritable bowel syndrome (IBS) since Ritchie's reports (1-3, cf. 4, 5). Presumably, this hypersensitivity is related to the pathogenesis of clinical pain symptoms. However, stable association with clinical bowel symptomatology was not found, and the identification of underlying pathophysiological mechanisms is still lacking. One reason for this situation could be that visceral pain is only a symptom secondary to other more basic mechanisms and, therefore, represents no pathophysiological marker of the syndrome. A second reason might lie in the heterogeneity of the syndrome defined solely by clinical criteria and exclusion of morphological and histological pathology. The resulting "functional" syndrome could combine different subgroups yet to be defined with different pathophysiological mechanisms producing very similar final symptomatology (cf. 6: Read's critique of clinical classifications of functional bowel disorders). Finally, conflicting results of earlier research could reflect technical and methodological problems encountered in assessing visceral pain mechanisms in humans, especially within the limitations of clinical studies.

It seems that a combination of these factors has blurred the current picture of the role of visceral pain sensitivity in IBS and of the mechanisms involved. After Ritchie's review (7) several replications of his findings on lowered thresholds for pain on distension appeared (8, 5, cf. 4), but a systematic investigation of compliance changes as a cause was not attempted until recently (e.g. 9-11).

The present study aimed at clarifying some of these points by following up on previous studies with additional technical and methodological precautions. It is based on a reanalysis of Ritchie's early attempts to identify peripheral causes of abdominal pain in IBS. His initial hypothesis of lowered bowel compliance as a major cause for the pain symptoms because of lowered distension tolerance was not fully supported by his results. However, they appeared to be complicated by methodological problems of group definition and compliance measurement. This caused him to abandon his compliance approach, and to look for contractile correlates of pain (spastic contractions, spontaneous or triggered by distension; cf. 3). However, a closer look at his original reports indicates that this may have been premature.

Pathophysiological heterogeneity of clinically defined IBS

Ritchie (1-3) compared patients with "irritable colon syndrome" (ICS or IBS) including constipated subjects with pain against healthy controls and constipated subjects without pain. He found lowered tolerance of tonic rectosigmoid distension in IBS patients. In the attempt to explain this finding by lowered compliance (measured as the diameter of the rectosigmoid after inflation with 60 ml air/atm.ref.), a complicated dispersion of subjects' data was found and interpreted as negative finding (1, p. 126). However, the bimodal distribution of colon diameters found at the standard inflation volume could also suggest a combination of two different subgroups one of them showing normal compliance of the rectosigmoid (cf. *Figure 1*). This is corroborated by the later report (3, Fig. 1, p. 627), where compliance was calculated as actual tension of the bowel wall at pain threshold.

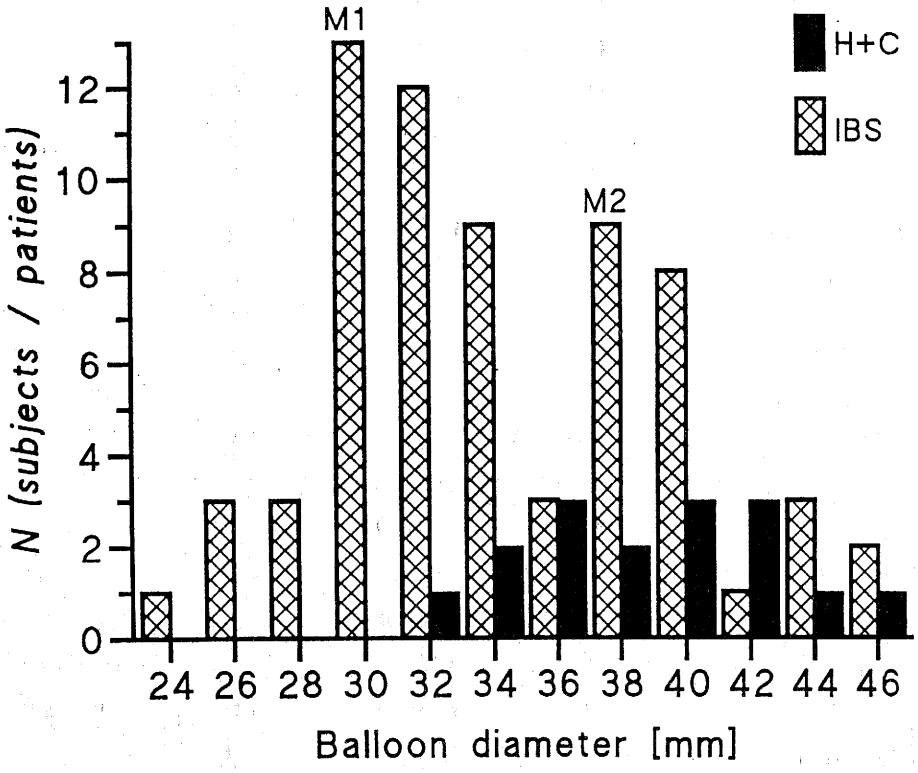

Figure 1: Colon diameter as index of compliance in IBS patients and control subjects after Ritchie (1).
Distribution of colon diameters at 60 ml inflation of balloon in rectosigmoid (25 cm ab anus) for 16 "control subjects" (H), that is, healthy subjects and patients with painless constipation (C) of unknown proportion (left); and for 67 patients with "irritable colon", that is, diarrhea and constipation patients, both with pain, in unknown proportion. M1, M2: submodes for possible subgroups (modified after Ritchie (1), Fig. 1, p. 126).

A possible explanation could be found in Ritchies combination of symptomatic subgroups in his experimental groups, that is, patients with diarrhea-predominant versus constipation-predominant bowel symptoms (and abdominal pain). It may be hypothesized that pain in constipated subjects differs in mechanism from pain in diarrheic patients, and that lowered compliance was not found in the former group. This would account for the second mode in the histogram of colon diameters. Although earlier work (e.g. 12) did not find such a differentiation, more recent data support the interpretation. For instance, different studies (13, 8, 11, 14) found differences in distension response of constipated vs. diarrheic patients. Prior et al. (9), in particular, found increased distension sensitivity in diarrheic, but not in constipated IBS patients.

This suggests that it is necessary to differentiate between symptomatic subgroups before investigating further into the pathophysiological mechanisms by which different aspects of the IBS symptomatology - altered bowel behavior and pain - are produced. It remains to be shown, however, whether sharper diagnostic criteria based solely on clinical information like the original Manning criteria (15) or the more recent subdifferentiation (16) of "functional bowel disorder" (FBD) and proper "irritable bowel syndrome" (IBS) will result in greater homogenity in terms of pathophysiological mechanisms. There seems to persist some disagreement on the question whether positive criteria of IBS can be defined in this way (17-20).

In addition to improving on clinical syndromatics of IBS diagnosis, a mechanism-oriented approach is necessary. It is addressed by Read's (6) critical reminder, that symptoms, particularly, abdominal pains "without organic cause", are only a final common result of several rather than specific correlates of singular pathophysiological processes, and that, therefore, diagnostic categories based on clinical criteria are often heterogeneous in terms of pathophysiology however elaborated. On the other hand, different aspects of the symptomatology like bowel symptoms (diarrhea, constipation) and abdominal pain may not share a common pathophysiological basis, and should be analysed separately. It is an empirical question, which combination of pathophysiological mechanisms would produce a given set of clinical symptoms or subsyndrome (diarrhea-predominant and constipation-predominant with or without pain, alternating bowel symptomes and so forth). For instance, pain in constipated patients may be quite different pathophysiologically from pain in diarrheic patients; similarly, constipation may be caused quite different in patients with or without pain and with and without diarrhea in alternation.

According to this approach group selection by clinical bowel and pain symptomatology is used only, in the present study, as a first homogenisation of the syndrome. It attempts to characterize a central part of the Irritable Bowel Syndrome (and a part of the wider category of Functional Bowel Disorder), that is, the *abdominal pain symptoms*, by reproducible physiological characteristics of sigmoid colon responses to distension on the one hand and by subjective (pain) responses on the other.

Increased sensitivity to experimental or physiological distension and/or generalized hypersensitivity to a wide variety of stimuli including humoral ones is most regularly found and widely reported in the literature (e.g. 21, 22, 12, 13, reviews: 23, 4). By contrast, results on motility changes correlated with pain have not been so unequivocable (e.g. 24, 25, 12, 26, 27, 14). Furthermore, visceral hypersensitivity may well be at the basis of some of the motility findings (28). Therefore, analysis of visceral hypersensitivity to distension seems to be a good starting point for pathophysiological analysis of IBS subcategories.

In the absence of morphological or histological changes or of signs of inflammation (by definition), it must be assumed that IBS pain is a correlate of functional changes for which the following candidates were discussed: (a) Pathological motility of some kind like irregular, "spastic" contractions, mass movements etc. (29, 12, 27); (b) tonically increased wall tension or "bowel tonus"; (c) increased tonic reflex response to distension by bowel contents usually not seen in phasic contractile activity. (d) "Passive" overstretch of smooth muscles (similar to migraine pain) or of adhering structures (omentum, pelvic floor) may also cause visceral pain (30). The resulting afferent nociceptive signal can either be correlated with (isometric) *wall* tension or with (isotonic) changes in *fibre-length* or both, depending on the kind of receptor involved and the way it is connected to the distended bowel (stretch receptors in series or parallel to the circular muscle fibres). Receptors in the longitudinal layer and the mesentery contribute to these stimulus dimensions, but the exact relations are not known (31). (e) A combination of different sources of abnormal mechanoreceptor stimulation was sometimes suggested to explain episodic acute pain in constipated patients (e.g. 7). (f) Finally, the pain symptoms may result from abnormal pain sensitivity (peripheral or central or "psychogenic") of origins yet unknown.

An unselected group of IBS patients contains varying percentages of patients with pains of different origins or mixed causation. For instance, it is very probable that different mechanisms are causing the pain symptoms associated with different bowel symptoms like diarrhea and constipation (7, cf. 12). IBS populations contain varying percentages of patients with diarrhea--predominant, constipation-predominant, and alternating bowel symptomatology, depending on gender composition, catchment area, route of referral and so forth. Thus, studies differing in these respects may produce quite different results in regard to correlates of abdominal pains.

In addition to differences between subgroups, interindividual differences in pain mechanism within subgroups must be expected on the same grounds. And, even within one patient with alternating bowel problems, pain mechanism may change from diarrhea and constipation episodes. Neglection of this and related complications explain well the conflicting picture in the literature. They point to the futility of attempts to identify one single local mechanism which could suffice to explain the different bowel symptoms and pains in all patients as the earlier concept of IBS as a pathophysiologically uniform "motility disorder" implied (cf. 23, but 4). *Reproducible function tests* are needed, which specify parameters of the visceral pain mechanism more directly and independently of clinical signs. During past years this was attempted by several groups through the use of continuous or stepwise distensions of the bowel by balloons or air inflation via coloscope (e.g. 32 and others). But matters remained complicated by unresolved technical and methodological problems such as insufficient reliability of clinical tests or incomplete specification of visceral pain parameters.

Sensory and non-sensory mechanisms of visceral pain

Apart of the questions discussed above, which are connected with identifying the physiological source of the assumed pathological mechanoreceptor stimulation in IBS, further and more fundamental problems relate to the complex nature of visceral *pain perception* itself which gives rise to abdominal *pain reports* of patients.

One class of questions concerns the specification of local transduction processes and the factors influencing the coupling of intraluminal volume and/or pressure-stimuli to the visceral receptors. For instance, the dynamic relationships between basal tonus (or tonic reflex intensity at a certain prestimulation diameter) and the afferent signal increment produced by a given diameter or pressure increment are by no means simple or even understood. This results in rather variable interoceptive transduction characteristics which can be changed over a large range of sensitivities by third variables like tonic innervation, smooth muscle tone etc. Analysis of visceral pain mechanisms in IBS therefore requires specification of transduction characteristics and the local biomechanical dynamics in case *local* changes yet undiscovered were causing the observed hypersensitivity to colonic distension. This possibility was not adequately considered in previous studies which often assumed silently that the visceral hypersensitivity of IBS patients was to be found either in receptor characteristics or the afferent path itself. Lowered distension tolerance was seldomly specified in terms of *volume* and *pressure* thresholds with simultaneous reports on *"compliance"* (pressure-volume characteristic). *Basal tonus* and *tonic* and *phasic reflex*

excitability are rarely estimated, and separation of *peripheral* and *central components* of visceral sensitivity was not attempted with one or two exceptions.

In addition to changes of peripheral transduction of distension stimuli, genuine changes of the sensitivity of afferent processing stages may still be involved. In that case, the number of possible candidates for pathological changes causing visceral hypersensitivity are multiplied. It is a well established fact in somatic pain research that sensory nociceptive signals are modified by central inhibitory processes which are additionally amplified by affective and cognitive-evaluative influences on pain perception at the cortical level (e.g. 33). Endogeneous pain control has been shown to play a particularly important role in visceral pain processing (34, 31, 35, 36). Instrumental pain behaviour which was suggested by several authors as an important determinant of symptom reports in IBS (e.g. 37), finally, could be another, relatively "late component" of such changes in pain processing. It remains to be shown, whether such non-sensory factors are needed to explain the clinical picture of visceral hypersensitivity in IBS, or whether changes in earlier sensory-perceptual stages account for most of the variance.

The problem of complex processing of the afferent signal in pain perception in general and in visceral pain in particular was largely neglected in the IBS literature. Only very simple comparisons of abdominal versus somatic pain sensitivity have been attempted. None of the published attempts including our own (e.g. 38, 5) can satisfy the rigid criteria of psychophysical pain assessment developed by pain research proper. In addition, pain thresholds and pain tolerance may vary independently and reflect quite different kinds of psychological influences on pain reports (39). This difference between "distension tolerance" and "distension (pain) threshold" was mostly not considered in the experimental protocols applied in the older but even in most recent publications cited above.

Obviously, more differentiated assessment of the processing stages of the visceral pain signal in IBS is needed. It is necessary to characterize, quantitatively and qualitatively, the different aspects of visceral pain mechanisms and of pain perception discussed and to show their psycho-pathophysiological revalence to symptomatology of different subgroups. In particular, sufficient specification and separation of the psychophysical relations involved is to be aimed at. They are discussed in the following paragraphs.

Assessment of peripheral stimulus transduction. The parameters of peripheral stimulus transduction in the bowel wall and the relations between volume and intraluminal pressure - the primary physical or "distal" stimulus - determine the actual receptor stimulation in terms of stretch force which produces the receptor signal and, finally, the resulting afferent message. In the case of visceral nociception, the characteristic of this transduction varies with prestimulus tone of the smooth muscle fibres. Heightened wall tension results in steeper slope of the pressure-volume characteristic for the transduction of distension stimuli, that is, in lowered apparent compliance. Consequently, painful wall tension is reached at lower distension volumes. Prestimulus tone, on the other hand, is a function of autonomic and enteric nerval tone, which is itself modified by the stimulus and the reflexive response to it by enteric neurones and muscle fibres, that is, by the enteric reflex excitability. The latter is under control of the autonomic innervation (apart from intrinsic enteric activity and g.i. peptides). Symptomatic subgroups in which this mechanism is responsible for the abdominal pain symptoms should be differentiated

by lowered pain thresholds to stepwise distension as well as higher bowel tonus and/or increased tonic response to colonic distension, that is, lowered compliance, from patients whose pain is caused otherwise.

To distinguish these peripheral components of visceral nociception, at least the biomechanical parameters must be recorded with satisfactory methodology. In the past, this was seldom achieved by the uncalibrated balloon-stimulation techniques available. On the other hand, the well-established and reliable methods of perfusion manometry do not produce biomechanical compliance estimates. Improved, calibratable distension balloons and adequate reproducible stimulation procedures are a prerequisite for this. One aim of the present study was to provide these techniques and apply it to the established compliance issue. The technical limitations set on assessment of visceral sensitivity and compliance have been discussed elsewhere in detail (40, 41). They comprise of the type of stimulation technique and precision of stimulus specification, the possibility to measure the relevant biomechanical variables in parallel, such as actual volume and/or pressure changes at the site of the distension, wall-tension, phasic and tonic response of bowel muscles, as well as static and dynamic compliance before, during, and after stimulation. Fidelity of balloon pressure and volume recordings necessary for these parameters was a major problem until very recently (cf. 41, for a comprehensive discussion of the physical relations involved and the technical requirements to be met).

Perceptual mechanisms. Primary sensations which are produced by a given afferent message, that is, the "proximal stimuli" in interoception, are themselves subject to further central processing by perceptual mechanism such as adaptation and contrast which operate on the interoceptive signal according to "psychometric functions" to produce the observed subjective experience reflected in the verbal report (42). It is to be expected that these processes are not simply identical with those known from somatic nociception. It is well known, for instance, that visceral nociception, different from somatic nociception, relies solely on central thresholds which decode critical intensities of visceral stimulation as "painful", because there are no high threshold receptors which could distinguish noxious from non-noxious stretch intensities like somatic nociceptors in skin and striate muscles. One must expect consequences for the psychophysics of visceral perception and pain. But almost nothing is known about the corresponding psychophysical functions.

Non-perceptual factors influencing clinical pain reports. From the rich literature on psychological factors in somatic pain perception, particularly in chronic clinical pain syndromes, one may well expect further differentiation by psychological factors, when clinical pain *reports* (distinguished from *perception*) of IBS patients have to be considered. As long as the specific mechanisms of visceral pain sensitivity discussed above are not characterized it would be premature to look for more general changes in pain perception of IBS patients. However, if changes at the peripheral transduction level or in afferent transmission can be ruled out, these high-level changes may be identified. Unfortunately, there exist no serious attempts to do so. A general lowering of (somatic as well as visceral) pain thresholds or an enhanced tendency to report pain may actually be involved in some patients, but as in research on chronic (somatic) pain patients, for instance, in low back pain, things may be more complicated (43). In fact, recent reports indicate, that somatic pain thresholds of IBS patients may be raised rather than

lowered (38, 5). Illness behavior and "operant" pain behavior will influence patient's complaints in addition as some authors have claimed (37). These components are difficult to isolate, but must be distinguished from perceptual processes as such.

Aims of study

(a) In conclusion of the above discussion a primary aim of the present study was to use stimulation and measurement techniques which would allow to characterize comprehensively the biomechanical dynamics at the colonic stimulation site in terms of pain thresholds to phasic and tonic distension to given volume stimuli under controlled pressure conditions and the constraints of clinical functional tests. At the same time a valid estimate of colon compliance (dynamic and static pressure-volume characteristics) and reliable recording of smooth muscle responses to the stimuli as well as asymptotic adaptation to increasing static distension volumes was to be made.

For this purpose suitable colon probes were constructed which could be applied "blind" and situated well up in the sigmoid colon or the descending colon by validated application routines with minimal discomfort and no radiation hazard. Calibrated cylindrical balloons were mounted on the probes which allowed controlled distension stimulation and compliance measurement as required. The techniques are described by Erasmus (44, 40, 41) (cf. sect. 2.2, below).[1]

(b) A central aim was to replicate the earlier results by Ritchie (1-3) on lowered distension tolerance (lowered volume and/or pressure thresholds for distension pain in the sigmoid colon) in IBS, but taking into account possible pathophysiological differences of symptomatic subgroups. Thus, patients with predominant constipation were to be compared with diarrhea-predominant patients and patients with alternating bowel symptoms as well as healthy controls. To avoid problems of diagnostic categories only patients with IBS diagnoses in the strict sense and with longstanding/recurrent, severe abdominal pain were to be included.

(c) The study tried also to answer the question whether differencies in distension tolerance between IBS patients and healthy controls as well as differences between those symptomatic subgroups of IBS could be explained solely by lowered compliance as previous studies suggested. By comparing phasic and tonic responses to experimental distensions information was to be gained about the specificity of the compliance mechanism if found, that is, whether lowered compliance might also explain differences in elicited contractile activity (primary and secondary contractions sensu 12).

(d) The correlation of lowered compliance and lowered distension tolerance with clinical pain symptoms was investigated to find out, whether and in which symptomatic subgroup the clinical pain may be explained by the compliance changes verified experimentally. In particular, differences between diarrhea- and constipation-predominant patients were expected in this respect.

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[1] The probe was developed out of earlier designs by Dr. F. Lederer, Univ. of Erlangen, which did not contain *calibrated* balloons for stimulation: Lederer F. Motilitätsmessungen im Gastrointestinaltrakt. Univ. of Erlangen, Medical Faculty, unpublished Dissertation for Habilitation, 1986. Earlier versions of the probes were described by Erasmus and Kröger (74, 48). They differ from the final construction of the stimulation probes described by Erasmus (40, 53) to some extend. Balloon properties, however, were the same, only these are relevant for the present study.

(e) Visceral and somatic pain sensitivity were to be compared over IBS subgroups and healthy controls to show whether lowered distension tolerance was a specific visceral phenomenon or was related to generally lowered pain thresholds and tolerance of "cold pressor pain" similar to the reports described above (38, 5).

METHOD

Subjects

Patient recruitment and selection criteria. *IBS patients* were selected from a larger sample of 247 patients who had been screened because of unexplained abdominal complaints, that is bowel dysfunction (diarrhea, constipation, or both) and pain, in the gastroenterology clinic of a Munich city hospital.[2] Part of them were referred by practitioners upon a circular sent to them, the greater part answered an advertisement in a local newspaper and were checked in the clinic. Only a few patients were accepted through the ambulance of the collaborating hospital. This avoided part of the problems encountered by previous studies in regard to the distorting effects of self-selection by clinic attenders. No reimbursement was payed to patients, but "bowel counseling" with a course in Progressive Relaxation (45) and a shortform of the behavioral pain treatment by Turk et al. (46) was offered on completion of the study. Informed consent was obtained from all participants during the initial phase of the screening. The entire protocol was approved by the City Hospital's board, and Helsinki regulations were observed throughout the study.

Most patients had had an earlier diagnosis of or were referred explicitly with a "functional bowel disorder" or "irritable colon" for further examination. Only those patients meeting Manning's criteria (15) except #3 ("pain relieve after flatus or bowel movement") and with distinct abdominal pain symptoms (duration $\geq$ 1 year; frequency $\geq$ 1/week; intensity $\geq$ 3 = middle-severe on a 5-point rating scale) were included in the final selection process. (Manning's criterion #3 was dropped, because it had been found to be not discriminative by several studies, e.g. 18, 47). Final selection started with a questionnaire on bowel complaints constructed on the basis of an earlier English version by Whitehead (unpubl; German version: 48), an extended anamnestic interview, and a sequential medical screening for yet undetected organic causes of the complaints. This consisted of general diagnostic measures to exclude organic disease (analysis of blood and faeces), rectoscopy, lower tract X-ray, and partial or full coloscopy in indicated cases. Patients with diarrhea were also tested for carbohydrate malabsorption, particularly, of lactose. Patients with ulcers, diverticula, or neoplastic growth as well as neurological or metabolic diseases were excluded. Finally, patients with psychiatric diagnoses of neurotic or endogeneous depression, anxiety disorders, or with regular use of antidepressives, neuroleptics, or tranquilizers, or with a Beck Depression Score > 20 were not included in the study to avoid

[2] Städtisches Krankenhaus München-Neuperlach, under Past Director, Prof. Dr. med. W. Ottenjann; present Director Prof. Dr. med. W. Schmitt.

involvement of the unresolved debate about the "psychosomatic" correlations in IBS populations (cf. 49 and others). This policy, together with the pain criterion above and the strict criteria for bowel symptoms, resulted in a selection very similar to "strictly defined IBS" as opposed to "functional bowel disorder" with the following exceptions: (a) Manning's criterion #3 dropped (see above), (b) somewhat stricter severity and chronicity requirements, and (c) explicit exclusion of identifiable psychopathology.

Definition of symptomatic subgroups. Patients meeting the criteria above were classified into three subgroups, that is, diarrhea-predominant (D: 15), constipation-predominant (C: 12), or alternating bowel symptoms (A: 19), according to their bowel problems as reflected in the questionnaire and an additional interview. *Diarrhea* criteria were (i) frequency for diarrheic episodes $\geq$ 1/month, (ii) duration of bowel problem $\geq$ 1 year, and (iii) *either* frequency of bowel movements in episode $\geq$ 2/day, *or* liquid/semiliquid consistency of stools. *Constipation* criteria were analoguous: (i) frequency of episodes $\geq$ 1/month, (ii) problem duration $\geq$ 1 year, and (iii) *either* frequency of bowel movement $\leq$ 1 in 2 days, *or* hard sheep-like stool consistency, *or* use of laxatives $\geq$ 1/week, *or* difficult or insufficient emptying. Patients were classified as having *alternating symptoms*, if they met both D and C criteria in alternating episodes.

65 patients met either one of these criteria *and* lay within the prespecified age range of 18 to 55 years. From this sample 50 patients were selected at random and assigned to the appropriate symptomatic group. It should be noted that gender distribution over symptom groups could not be controlled satisfactorily by this procedure (cf. Table 1).

Selection of controls. Healthy control subjects (H) were recruited by advertisement. 231 answered, 162 matched to patients from the clinical sample according to age and sex. They received the questionnaire on bowel complaints and Beck's Depression inventory (BDI). Those with somatic complaints, a BDI score above 20, or a history of psychological problems or substance abuse were excluded. Out of the remaining 72 subjects 14 matched controls were selected. Control subjects were paid for participation.

Table 1 summarizes demographic data (age, sex, social status), clinical characteristics, and psychometric indices of the four resulting experimental groups. It shows also that there is a tendency to slightly increased depression and anxiety scores in all patients subgroups (Kruskal-Wallis test, $p < 0.05$), despite exclusion of persons with psychopathological signs detectable in the standardized interview and/or clinical history. Whether this difference could have had effects on the visceral pain results is discussed in subsequent selections. Systematic group differences in other variables of Table 1 were not found.

Variable		Controls (H)	IBS pat. (C + D + A)	Constip.-predom. (C)	Diarrhea-predom. (D)	Alternating sympt. (A)
N		14	46	12	15	19
Demographics (%):						
Sex	F	42,9	57,5	81,8	46,2	44,5
	M	57,1	42,5	18,2	53,8	55,5
Age	0-20	0,0	2,5	0,0	0,0	7,5
	21-40	30,8	45,0	54,5	46,2	34,3
	41-60 yrs	69,2	52,5	45,5	53,8	58,2
Family state	unmarried	38,4	39,3	50,0	30,0	37,9
	married	30,8	46,4	33,3	60,0	45,9
	wid./div./sep.	30,8	14,3	16,7	10,0	16,2
Education	elem. sch.	0,0	2,9	0,0	0,0	8,7
	prof. school	23,1	17,6	25,0	9,0	18,8
	sec. school	30,8	35,3	25,0	45,5	35,4
	university	46,1	44,7	50,0	45,5	37,1
Occupation	student	23,1	5,1	9,1	0,0	6,2
	houseperson	30,8	5,1	0,0	7,7	7,6
	employee	46,1	74,4	81,8	74,3	67,1
	civil servant	0,0	12,8	9,1	15,4	13,9
	self-employed	0,0	2,6	0,0	2,6	5,2
Bowel symptoms (%):						
Diarrhea episodes [b]	continuously	-	35,0	0,0	44,4	27,3
	1 / week	-	60,0	0,0	55,6	63,6
	≤ 1 / month	-	15,0	0,0	0,0	9,1
Constipation episodes [b]	continuously	-	39,0	71,4	0,0	10,0
	1 / week	-	30,5	14,3	50,0	90,0
	≤ 1 / month	-	30,5	14,3	50,0	0,0
Feeling of incomplete evacuation	never	-	16,7	28,5	14,3	7,3
	rarely	-	45,8	43,0	57,1	37,3
	often	-	37,5	28,5	28,6	55,4
Abdominal pain (%):						
Frequency	continuously	-	20,8	60,0	0,0	2,4
	daily	-	41,7	20,0	87,5	17,6
	1 / week	-	25,0	20,0	12,5	42,5
	1 / month	-	12,5	0,0	0,0	37,5
Intensity [c]	weak	-	4,0	0,0	12,0	0,0
	tolerable	-	36,0	40,0	38,0	30,0
	strong	-	60,0	60,0	50,0	70,0
Psychometrics (mean scores) [d]						
Beck-Depression Score		5,1	8,5	7,2	8,4	9,9
Trait-anxiety (Spielberger)		32,5	46,3	44,2	47,5	47,1

[a] N = 60; see text for selection criteria.

[b] Definition of diarrhea and constipation episodes: see text.

[c] 3-point rating scale in Questionnaire of GI Symptoms, Note 3.

[d] Only psychometric data on psychopathological dimensions are given here. Clinically relevant psychopathology was excluded as described in the method section.

Table 1: Demographic, clinical, and psychometric characteristics of IBS patients and controls.

Apparatus

Basically the same apparatus as described by Erasmus (41) was used for stimulation of the sigmoid colon and recording of tonic and phasic responses. It consisted of a "combination probe" with a calibrated latex balloon of flat pressure-volume characteristic between two recording sites and suitable transducers and amplifiers for manometric and electromyographic recording (*Figure 2*)[3]. A semi-automatic gas syringe triggered manually was used for applying the distension stimuli instead of the automatic equipment described by Erasmus (41).

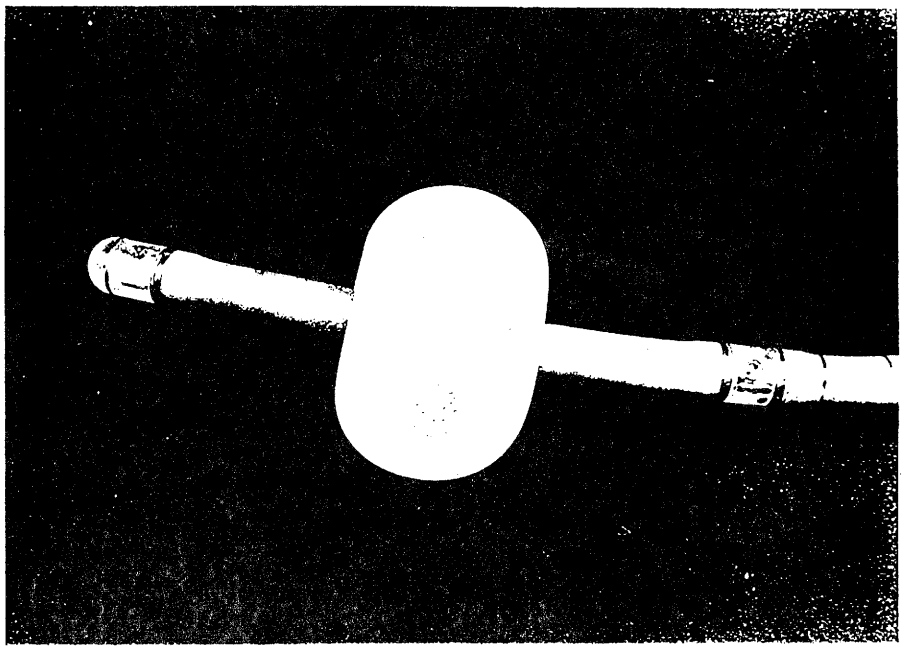

Figure 2: Colon probe for simultaneous recording and stimulation.
From Erasmus (40), with permission; cf. (41).

Air-filled balloons were preferred over liquid filling for technical as well as safety reasons (lowest flow resistance and operation pressures). Balloon properties for reproducible stimulation of specified volume and pressure-values with valid recording of bowel response were achieved by mounting in pre-stretched condition and individual calibration of diameter-filling functions. This ensures flat and specified pressure-volume characteristics over a wide range of distension volumes and allows adequate correction of pressure-volume readings with specified balloon diameters which is a prerequisite of veridical compliance estimation in vivo (cf. 40, 41, for technical details).

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[3]The probe was developed out of earlier designs by Dr. F. Lederer, University of Erlangen, which did not contain *calibrated* balloons for stimulation: Lederer F. Motilitätsmessungen im Gastrointestinaltrakt. Univ. of Erlangen, Medical Faculty, unpublished Dissertation for Habilitation. Earlier versions of the probes were described by Erasmus and Kröger (74, 48). The differ from the final construction of the stimulation probes described by Erasmus (40, 53) to some extend. Balloon properties, however, were the same, only these are relevant for the present study.

Manometric and electric recordings were done with standard transducer and amplifier equipment. Data were recorded on a 16-channel PCM tape-recorder for off-line analysis on the laboratory computer (PDP 11/44, Digital Equipment Corp.). The whole experiment including trigger signals for the recording tape and the syringe operation was controlled by digital logic.

For assessement of somatic pain sensitivity by the Cold Pressor Test a basin with freshly crushed ice suspended in as little water as possible was used to ensure 0 °C throughout the procedure. Skin temperature was measured during left hand immersion and after withdrawal by a temperature sensor which was in direct contact with the skin but encapsulated against the surrounding ice-water or air, respectively. Duration of hand immersion as well as temperature at withdrawal were controlled on the polygraph recording.

Procedure

Subject preparation. On completion of the initial investigations described above subjects received final information on the distension study together with the exact date of the session and three Haemoccult™ test-envelopes. They were to be applied on three consecutive days before the session. If one of them was positive, an additional sigmoidoscopy was performed. If necessary the session was cancelled. Subjects obtained two ampullas of a mild enema (sodium mono-/diphosophate, Fresenius™, together 260 ml) with which they had to clean the rectosigmoid on the morning of the day of measurement. On arrival, subjects were asked to attempt evacuation. The procedure, together with detailed instructions on meal restrictions (last meal not later than 6 p.m., no heavy fatty food, no gas producing food like beans or onions etc. on day before measurement), was sufficient to reduce feces in rectum and sigmoid to a degree compatible with stable probe application and good recordings in most cases. Only rarely was an additional enema (max. 100 ml) necessary on site before measurement.

After these preparatory steps the colon probe was applied (mid sigmoid, tip of probe 30 cm, balloon 20 cm ab anus) without direct sonographic or X-ray control. Previous tests had shown that, because of the relative large diameter of the probe (14 mm) with rounded tip and its semi-flexibility, this procedure is safe. At the same time positioning is sufficiently precise, and curling back does not occur because of the residual stiffness due to the multi-lumen core of the probe (41). In addition, position was controlled by activity pattern and absence of urge to defecate upon tonic suprathreshold distension.

Experimental procedure. To evaluate tonic responses to distension and visceral pain thresholds a modification of the graduated distension test by Ritchie (1, 2, cf. "Introduction") was used, which is similar to Whitehead's procedure (12,5): After a small prefilling of the balloon (basal volume, BV = 10 ml), the balloon is inflated by 20 ml of air (atmosph. ref.) every 2 min until first discomfort and, finally, slight pain is reported. However, in any case not more than 10 inflations (maximal end-volume = 210 ml) are given. For additional safety an absolute pressure limit of 150 hPa is observed.

The subject is asked about the quality and intensity of the sensations produced after each distension at the end of the 2 min-interval ("distension felt", "pressure", "pain", "urge to defecate", and "sense of fullness") by 5-point rating scales on a checklist filled in by the

experimenter. At the end of the whole series retrospective ratings on these perceptive dimensions and additional questions on location etc. were asked.

Recordings and data analysis

Balloon pressure, motility recordings and compliance measurements. Tonic (static) pressure responses, Δp, as well as phasic (contractile) activity after stimulation (primary and secondary contractions, PC and SC, according to 12) at the stimulation site were recorded from the balloon. Conventional perfusion manometry proximally and distally from the balloon was also performed to control for elicited motility more distant to the stimulation site and contraction waves travelling rostrally or caudally. Background and elicited electrical activity was recorded from the same sites as manometric signals and analysed by spectral analysis and wave-to-wave evaluation (cf. 50, for description of analysis).

Tonic pressure response, Δp, was defined as the remaining rise in balloon pressure per inflation after 2 min (*Figure 3*). Averages of Δp to the first 4 inflations were used as index of apparent compliance, CI.[4] It may also be considered as an index of *tonic* bowel reflex excitability. Amplitude of primary contraction, PCA, secondary contractions SCI (calculated as sum of square secondary contraction amplitudes over the rest of the 2 min interval), and amplitude of maximal secondary contraction (SCA_{max}) served as index of *phasic* reflex excitability (cf. *Figure 3*). Corresponding indices for perfusion channels were calculated analoguously.

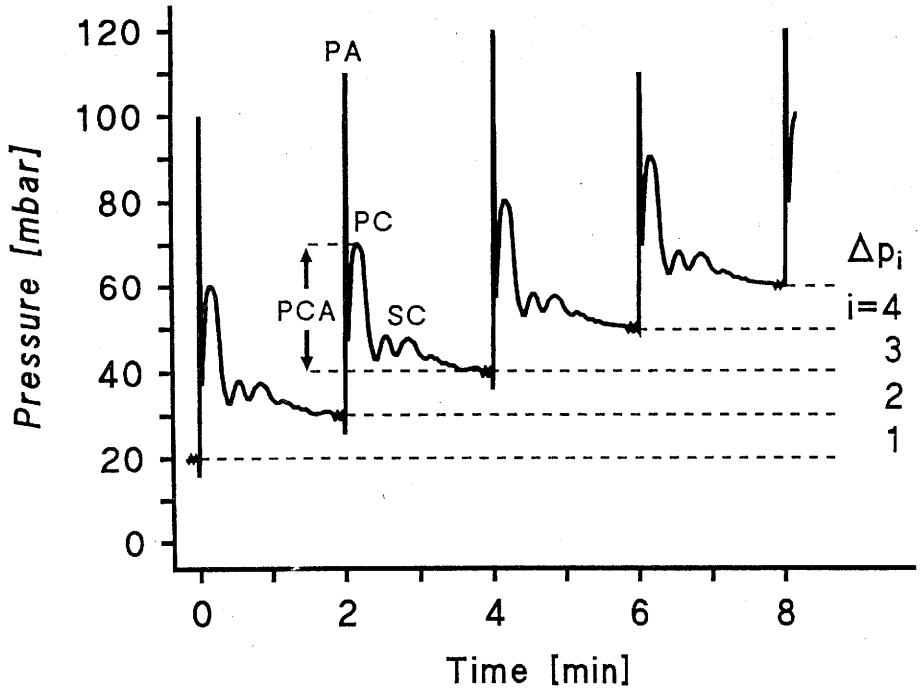


Figure 3: Definition of tonic and phasic pressure responses in graded distension test.

Δp_i = asymptotic pressure rise at i-th inflation (20 ml steps, air ref.). Averages of the first 4 inflations (after a basal filling volume of 10 ml) were used as index of pressure response or "bowel reflex tonus" or tonic compliance index. PCA = amplitude of primary, SCA = amplitude of secondary contractions; PA = pump artifact.

[4] CI = Δp/ΔV; with ΔV = 20 ml = const.: Δp ~ CI.

Perception data. Data on "distension felt", "pressure", "discomfort", and "pain" sensations as well as ratings of "urge to defecate" and "fullness" were obtained on 5-point rating scales as described. This paper is based mainly on threshold volumes and pressures for first pain report ("just painful" after first report of discomfort; see above). Absolute detection thresholds for distension cannot be determined very reliably with the usual GDT protocol because they lie near or below its resolution ($\approx$ 8 ml), and reliable threshold estimation would require at least several repetitions of a given stimulus volume. Consequently, where it was attempted (e.g. 12, 5), generally no differentiation between IBS or subgroups of IBS and controls were found. Similar limitations hold for thresholds of subjectively felt "pressure". Therefore, results of subjective ratings during and after the GDT are used for additional confirmation only.

Somatic pain sensitivity was assessed as cold pain threshold, $t_{cp.0}$ = time until first pain sensation after immersion of the hand into the icewater, cold pain tolerance, $t_{cp.w}$ = time until hand withdrawal, skin temperature at withdrawal, T_w, and the subjective pain-rating, P_{sr}, before withdrawal on a 4-point category-scale (no pain to strong pain). These measurements were taken in a separate session with no colon probe applied.

RESULTS

Volume thresholds for pain report[5]

As expected, inflation volumes (atm. ref.) at which first pain appeared differentiated between IBS patients, C + D + A, and normal controls, H ($p < 0.0005$ for the omnibus-test by non-parametric analysis of variance, Kruskal-Wallis test). However, only patients with diarrhea (D and A) were responsible for these differences (*Figure 4*): Constipated IBS patients (C) did not differ from controls, patients with diarrhea-predominant (D) and alternating symptoms (A) did not differ from each other. The differences between these two pairs of groups where highly significant ($p < 0.0001$; Mann-Whitney U-test; cf. Table 2).

Volume of distending balloon at first pain report in stepwise distension test; individual values (dots) and group medians (long bars) + first/third quartiles (short bars). Stepwise distensions consisted of 20 ml inflations (within 1 s) after 10 ml prefilling of the stimulation balloon. Stimulation probe according to Erasmus (74); cf. (41). H = controls (19); C = constipation-predominant IBS patients (12); D = diarrhea-predominant IBS patients (15); A = IBS patients with alternating symptoms (19). *Significance:* $p < 0.001$ for the overall group effect (Kruskal-Wallis nonparametric analysis of variance) and for the difference between (H + C) vs. (D + A) (Mann-Whitney/U-test); cf. Table 2.

[5]Part of these and the following data were obtained by C. Kröger (48) and L.-P. Erasmus (40) for their Ph.D. theses, University of Tübingen, Germany.

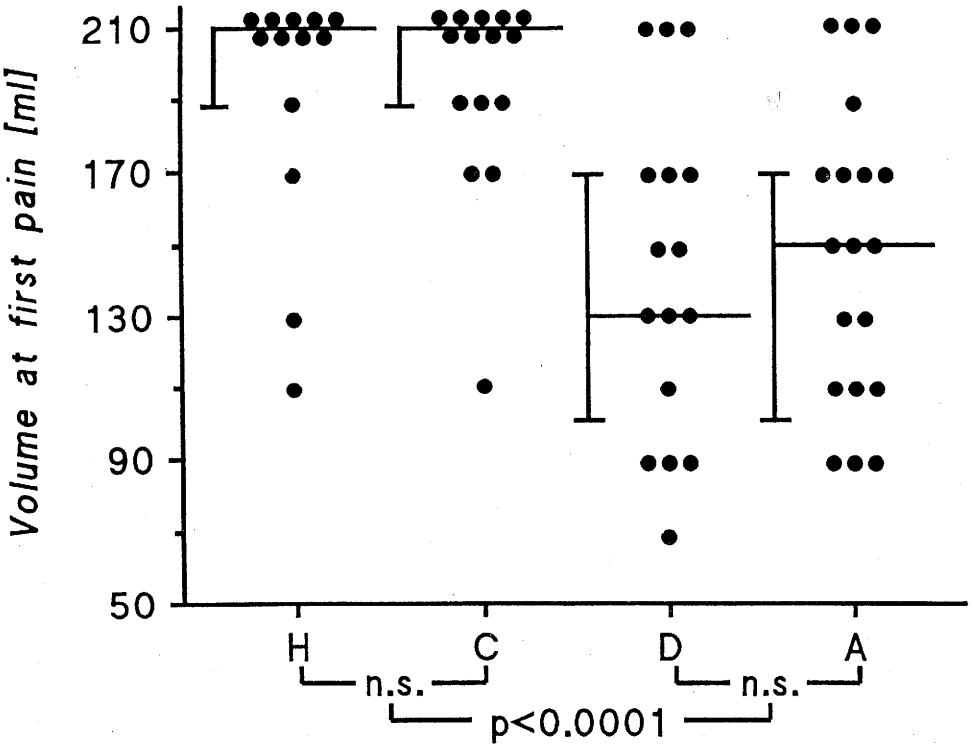


Figure 4: Distension pain in symptomatic subgroups of IBS and control subjects.

Variable	Omnibus-Test of group-effects (Kruskal-Wallis H-Test)	Single comparisons (Mann-Whitney U-Test)			
		H vs. IBS	H vs. C	D vs. A	H+C vs. D+A
VT	0.0005	0.02	n.s.	n.s.	0.0001
CI	0.002	n.s.	n.s.	n.s.	0.0001
PT	0.002	n.s.	0.05	n.s.	0.0002
PCA PCA*	0.05 n.s.	n.s. n.s.	n.s. n.s.	n.s. n.s.	0.005 n.s.
SCI SCI*	0.02 n.s.	n.s. n.s.	n.s. n.s.	n.s. n.s.	0.01 n.s.
CPT	-	n.s.	-	-	-

VT: Volume threshold of pain
CI: Compliance index
PT: Pressure threshold of pain
PCA: Primary contraction amplitude
PCA*: PCA corrected for CI-effect by regression transformation
SCI: Secondary contraction intensity
SCI*: SCI corrected for CI-effect by regression transformation
CPT: Cold Pressure tolerance

Table 2: Overview of results and statistical analysis.

Tonic pressure response and apparent compliance

Δp-values showed a complementary pattern of differences between IBS subgroups and controls: Patients with diarrhea-predominant and alternating symptomatology showed steeper pressure rises in accordance with their higher visceral pain sensitivity (Kruskal-Wallis test for the group effect: $p < 0.002$; Mann-Whitney U-test for the difference between H + C and D + A as above: $p < 0.0001$; cf. Table 2). *Figure 5* presents the results as compliance index, CI, equal to pressure rise per volume change [hPa/ml], averaged over the first four distensions (cf. "Method").

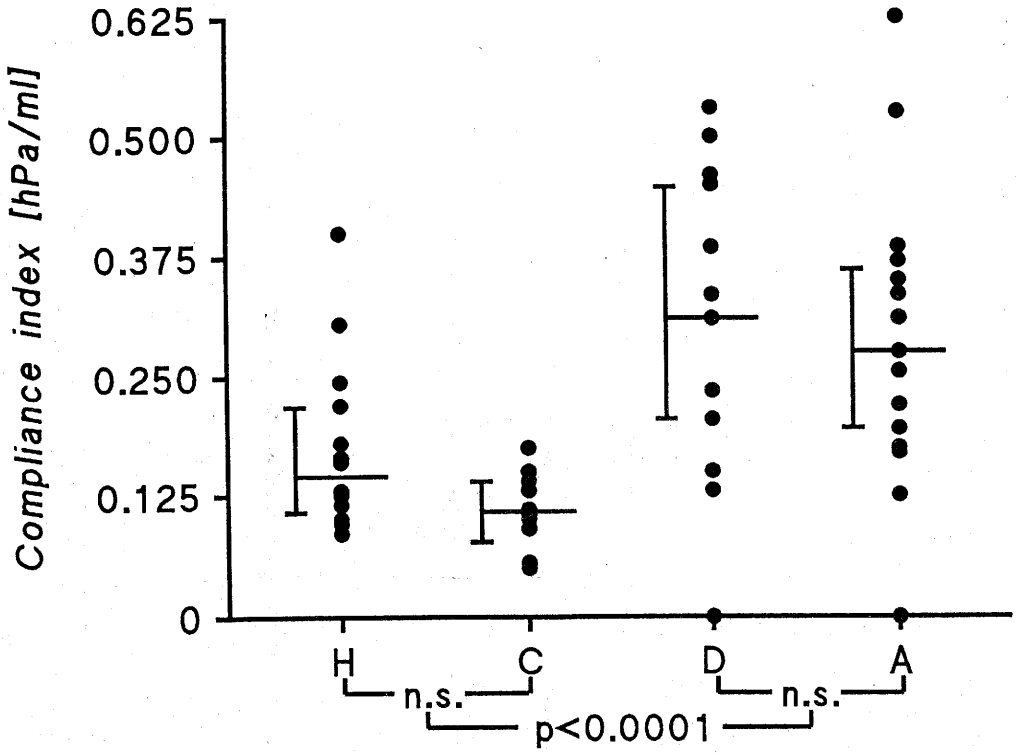


Figure 5: Compliance of sigmoid colon in IBS subgroups and controls.
Experimental groups as in Figure 5. Compliance is depicted as average pressure rise over distension volume (hPa/ml) for the first 4 distension steps (end volume = 90 ml, with 10 ml prefilling). *Significance:* $p < 0.002$ for the overall group effect, Kruskal-Wallis test; $p < 0.0001$ for the difference between (H + C) vs. (D + A), Mann-Whitney-U test. See text for explanation.

Relation between pain thresholds and colonic compliance

Correlations and two-way discriminance between IBS subgroups. The complementary relation of distension tolerance and compliance differences suggests that the latter may account for the differences in distension tolerance when measured as volume at first pain report. This interpretation is corroborated by their significant negative correlation ($r = -0.49$; $p < 0.05$). The correlation is only moderate, however. A possible explanation for this may be derived from the two-way scatter diagram of *Figure 6*: It shows that the overall correlation is due mainly to the dispersion of tolerance-compliance pairs over the different subgroups, while intragroup correlation is much lower. It is significant only within the combined diarrhea groups (D + A; $r = -0.37$, $p < 0.05$), but not within control and constipated groups (H + C; $r = +0.12$, n.s.)

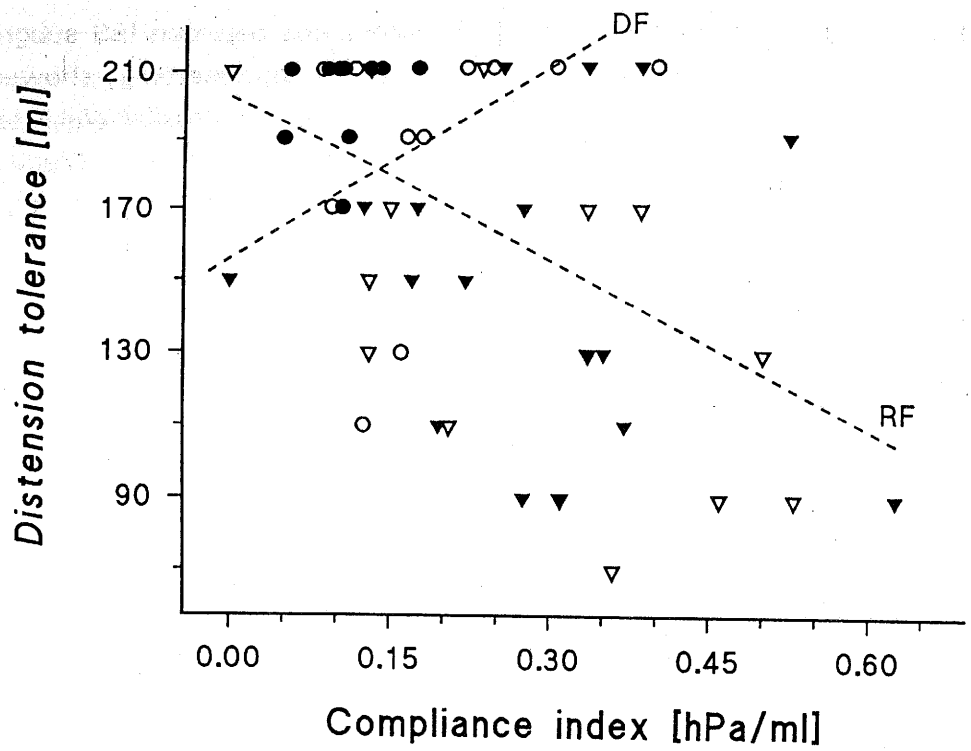


Figure 6: Correlation between distension tolerance and compliance in IBS subgroups and controls.
Two-dimensional scatter-diagram of distension volume at which first pain-report occurred over compliance-estimate CI (cf. Figure 6). ○ = H, □ = C, ● = D, ■ = A. RF: Regression function VT = -155,45 ml²/hPa • CI + 202,28 ml. Overall correlation = -0.49; intraclass correlations for (D + A) and (H + C) = -0.37 ($p < 0.05$) and 0.12 (n.s.), respectively.
DF: Linear discriminant function between (D + A) and (H + C); 0.0166 • VT + 7.8493 + CI = 4.1168.

This means that *lowered bowel compliance explains lowered distension tolerance only in IBS patients with diarrhea and alternating bowel symptoms, but not in constipated patients*. Even in the D and A patients, however, the correlation is not high. Therefore, distension tolerance must contain another component in addition to variations in biomechanical characteristics of bowel wall or visceral reflex tonus. This is corroborated by a linear two-dimensional discriminant analysis between (D + C) and (H + C) subgroups using CI and VT as classification variables (method of group centroids, 51): VT alone discriminates better than CI alone, and their combination is better than VT alone. The improvement concerns mainly the sensitivity (6 %) and the predictive accuracy of the classification (5 % for the negative diagnosis, 2 % for the overall classification), but not its specificity.[6] *Table 3* shows that the discriminant power is quite high in general with no coefficient below 0.80 when VT and CI are combined. Considering the small group size, however, one must be cautious in interpreting these coefficients before cross-validation with a second and larger sample.

[6] Sensitivity and specificity are defined as usual, that is, proportion of individuals with a priori diagnosis D or A, and proportion of C or H individuals, respectively, which are found by the GDT relative to the actual proportions in the sample. Predictive accuracies are calculated similiarly but relative to the total number of subjects. See (51) or equivalent standard texts on multivariant analysis.

Discrimination measures *)	Predictors		
	VT alone	CI alone	VT x CI
Cutoff	185 ml	0.17 hPa/ml	see DF **)
Sensitivity	0.82 ***)	0.76	0.88
Specificity	0.85	0.77	0.81
Predict. accuracy (overall)	0.83	0.77	0.85
Predict. accuracy (pos. = H + C)	0.79	0.71	0.84
Predict. accuracy (neg. = D + A)	0.88	0.81	0.86

*) Definitions: note 5
**) Discriminant function: $Y = 0.0166 \cdot VT + 7.8493 \cdot CI - 4.1168$
***) $\chi^2 = 28{,}864$, $p < 1 \cdot 10^{-7}$

Table 3: Two-way discriminance of GDT variables.

Volume versus pressure tolerance. The most likely source of the unexplained variance in distension tolerance seems to be *genuine sensitivity differences* between subgroups and in individual patients. They could stem from differences in receptor sensitivity, responsivity of afferent visceral neurons at the spinal level or altered central processing of visceral signals. Changes in psychological adaptation to altered visceral input as earlier suggested by some authors (e.g. 26, 37) might also play a role in these patients (cf. "Introduction"). Pressure values at the point when first pain report occurs can clarify this question, because intraluminal pressure is supposed to be closely related to one class of adequate stimuli, that is, forces on the receptors involved. The method of pressure and diameter calibration of balloons used in this study allows assessment of pressure tolerance independently of volume tolerance.

Figure 7 shows that in fact differences in pressure tolerance may be found. The pattern of differences, however, is unexpected, at least in view of previous reports in the literature, which did report both types of distension thresholds in conjunction: D and A groups showed significantly *higher intraluminal pressures* at the volume at which pain was first reported than H and C groups (Kruskal-Wallis for the omnibus test: $p < 0.002$; U-test for the paired group differences: $p < 0.0002$).

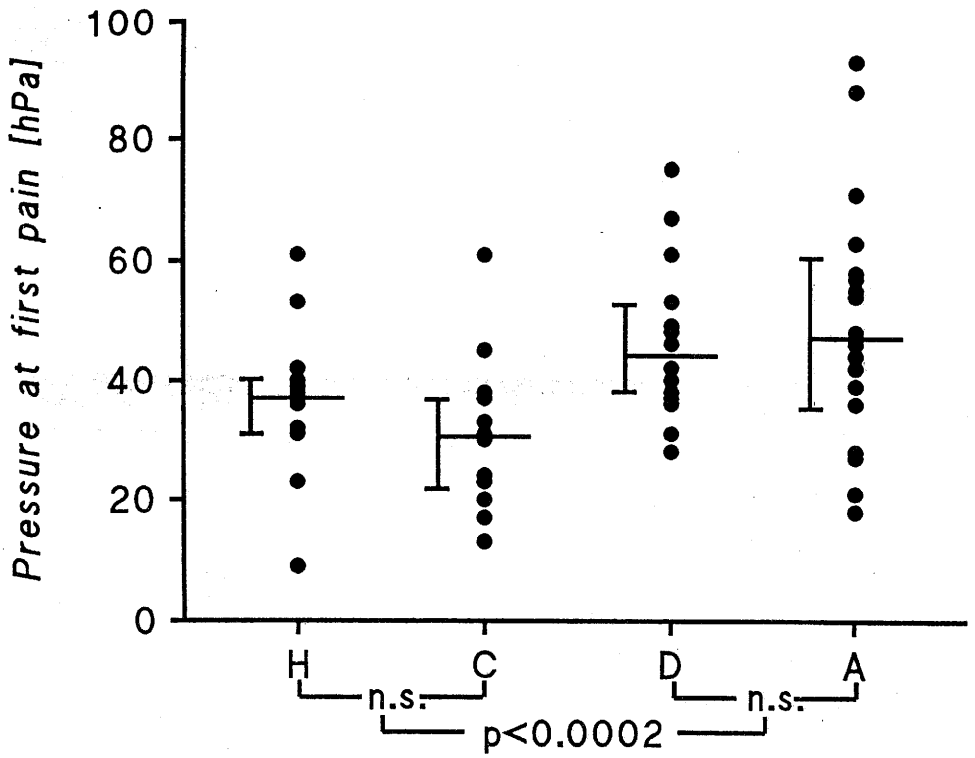


Figure 7: Intraluminal pressures at first pain report in IBS subgroups and controls.
Visceral pain thresholds in terms of intraluminal pressures, corrected for basal pressure at prefilling volume (10 ml). Subgroups as in previous figures. *Significance:* $p < 0.002$ for the overall group effect, Kruskal-Wallis test; $p < 0.0002$ for the difference between (H + C) vs. (D + A), Mann-Whitney-U test.

This result clearly contradicts the notion that IBS-patients show visceral hypersensibility. In contrast, tolerance for intraluminal pressures is *increased* in those patients who show general lowered volume tolerance (D and A). The latter, then, must be an effect of compliance lowered sufficiently to overcompensate for the heightened pressure threshold. This may reflect long-term adaptation to increased intraluminal pressure values because of the lowered bowel compliance. Figure 7 also shows that, despite highly significant differences between subgroups, variations in pressure tolerance are still substantial. Therefore, *differences in (genuine) visceral sensibility as well as bowel compliance are needed to account for the total variance of sensitivity against tonic distension of the bowel.*

The result sheds some light on the seeming contradictions between earlier and recent reports on visceral hypersensibility of IBS patients: When subgroup differences, variations in compliance, and pressure tolerance are considered together a clearer picture of differences appears. This is illustrated by the *characteristic curves for visceral pain* (probability of pain as a function of distension volume and intraluminal pressure) in *Figure 8*. These curves comment also on the pioneering results by Ritchie (1-3, 7) who used similar displays.

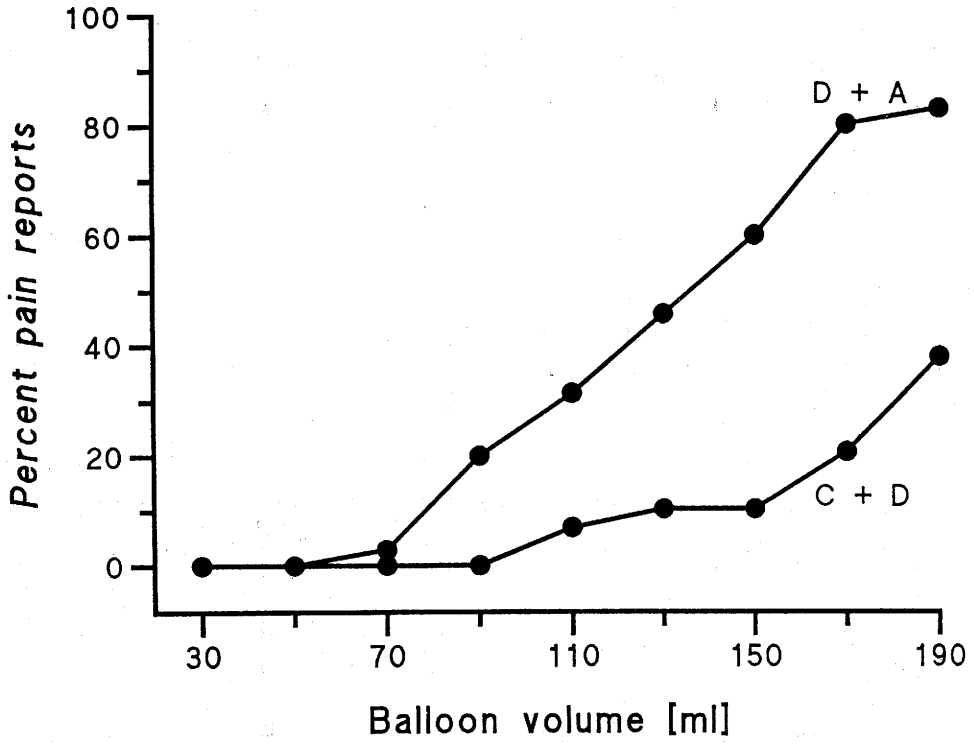
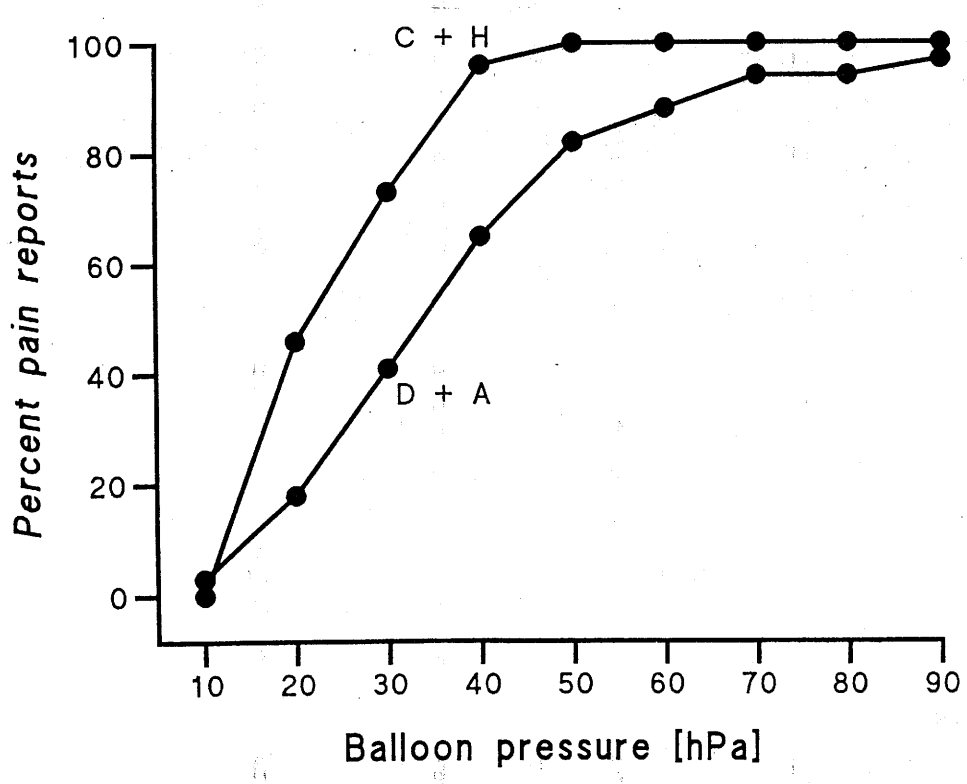


Figure 8: Psychophysical functions of pain sensations.

a: Percentage of pain reports in diarrhea subgroups (D + A) compared to controls and constipated patients (H + C) as a function of balloon volume; same data as in Figure 5, rearranged according to Ritchie (1), Fig. 2.



b: Percentage of pain reports as a function of intraluminal pressure (corrected).

Primary and secondary contractions

While the results described above demonstrate that tonic responses to tonic distension play a crucial role in production of the apparent hypersensitivity to mechanical stimuli found in IBS, they do not rule out hypernormal phasic reflex contractions as basic or at least additional factors as suggested, for instance, by Ritchie (7). In the present study Whitehead's method of stepwise distension instead of Ritchie's continuous inflation was used (12) to allow investigation of the effect of reflex contractions to (phasic) distension in addition to tonic responses. The method provides an adequate input to phasic receptors at the rising slope of the distension step.

Evaluation of primary contractions to the distension step (PCA) and secondary contractions ($SCI = \Sigma SCA_i^2$) during adaptation to the new volume showed group differences corresponding to the findings of lowered volume tolerance as well as compliance values (*Figure 9*). Group differences were highly significant for both PCA and SCI (Table 2) and showed a grouping pattern mirroring that of the tonic indices: *(D = A) > (C = H)*.

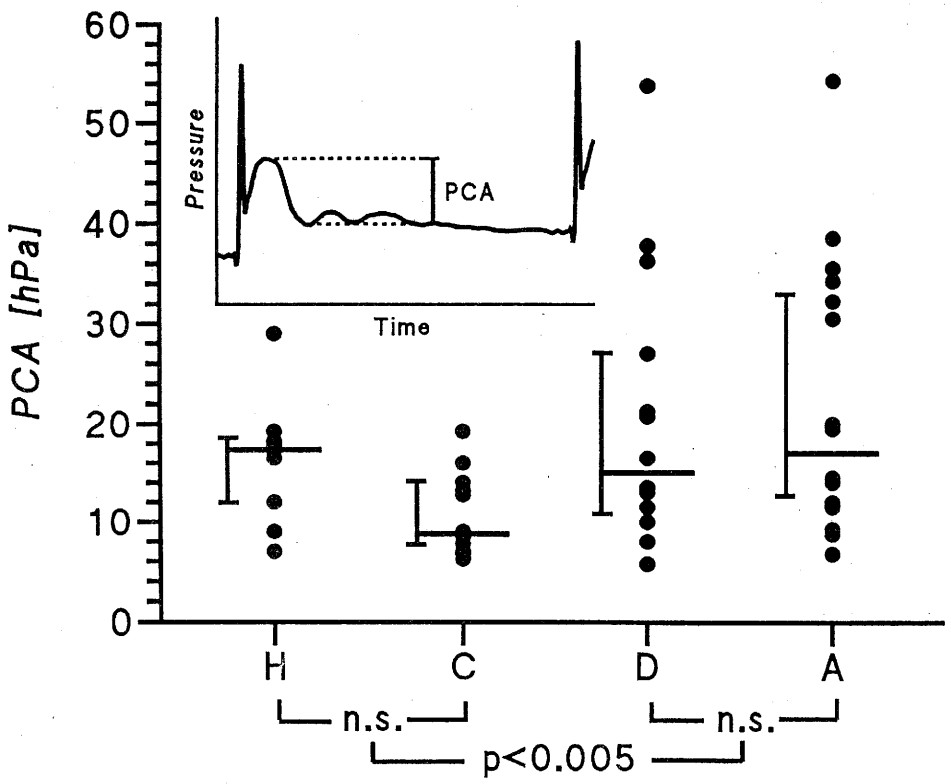
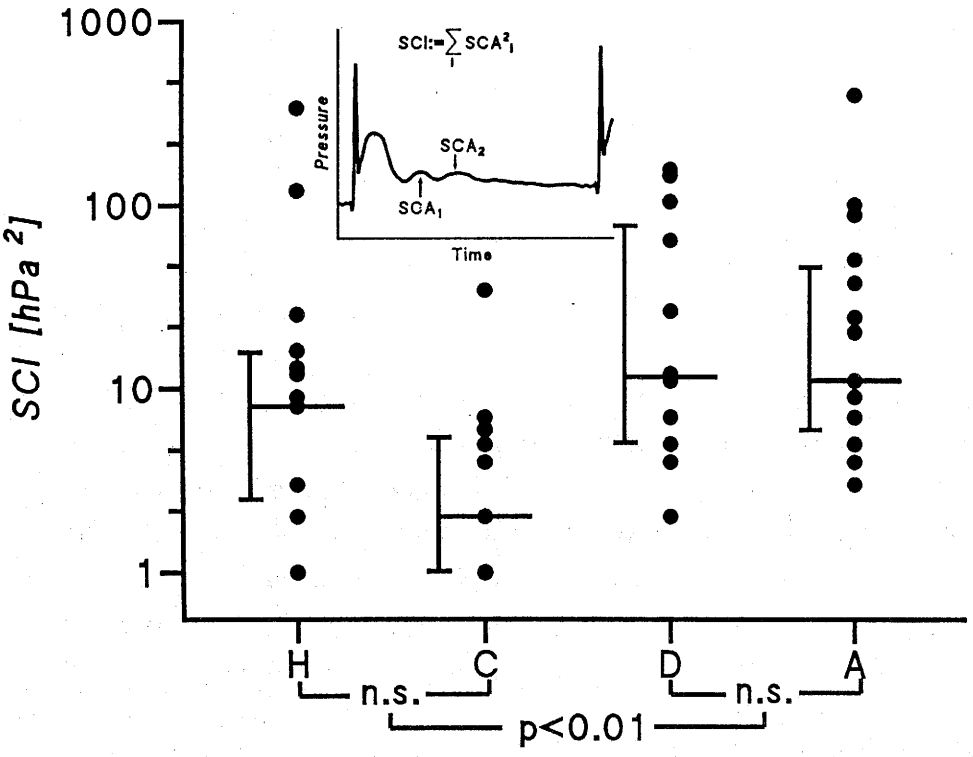


Figure 9: Primary and secondary contractions to stepwise distensions in IBS subgroups and controls.

a: Average amplitudes of primary contractions (PCA) to first 4 distensions (20 ml steps). Definition of PCA according to inset. *Significance:* $p < 0.05$ for the overall group effect, Kruskal-Wallis test; $p < 0.005$ for the difference between (H + C) vs. (D + A), Mann-Whitney-U test; no significant differences after correction for component explained by compliance differences (= covariate). See text for further explanation.



b: Secondary contractions to stepwise distensions in IBS subgroups and controls measured by sum of squared amplitudes of contractions > 1 hPa (PCA excluded); SCI = average over first 4 distensions. This measure is monotonically related to the conventional motility index, MI. *Significance:* $p < 0.02$ for the overall group effect, Kruskal-Wallis test; $p < 0.01$ for the difference between (H + C) vs. (D + A), Mann-Whitney-U test. No significant differences after correction for component explained by compliance differences (= covariate). See text for further explanation.

However, correlations of these measures with the compliance index were significant if moderate (0.43 and 0.60). Therefore, correction for that part of the contraction indices which is explained by the differences in bowel compliance seemed appropriate. This was done by the method of regression transformation which is logically equivalent to an analysis of covariance with compliance as covariate. The correction for compliance effects resulted in total disappearance of all significant differences of contraction indices between groups and subgroups indicating that reported differences in reflex contractions to distension may be explained by simple mechanical relations between pressure-volume characteristics of the bowel and amplitude measures of contractile activity like motility indices etc. (see "Discussion"). This, of course, cannot be generalized to those studies which used simple counts of (secondary) contractions as dependent measures (e.g. 12). The issue is not finally resolved, therefore.

Motility recordings at the electromanometric recordings rostrally and caudally of the stimulation balloon generally showed very few significant and inconsistent effects between IBS patients and controls, no significant differences between subgroups or between subgroup pairs characterized by their GDT distinctions as above (results described in detail in Löffler, 50).

Specificity of lowered pain thresholds

To clarify whether the differences in distension thresholds for pain sensations are fully explained by the peripheral compliance mechanism as suggested, consideration of thresholds for non-nociceptive sensation is helpful. The most prevalent view on visceral pain mechanism in current physiological research holds that - differently from somatic pain - there are no pain-specific, that is, high-threshold mechanoreceptors for visceral pain, which would directly encode pain, at least not in the bladder, colon and most parts of the g.i.t. (52, 30 but 31). Instead central threshold neurons must decode the intensity-frequency code of afferent signals from receptors sensitive to the full range of distension stimuli from sensation threshold to strong pain. This view would suggest that visceral hyperalgesia based on a peripheral physiological mechanism must be paralleled by a general visceral hypersensitivity to be seen in volume thresholds for non-nociceptive sensations ("just felt", "slightly unpleasant sense of pressure etc., but not painful"; see "Method"). Therefore volume thresholds for non-nociceptive sensations were also compared.

No significant differences ($p = 0.153$; one-way ANOVA) in *sensation thresholds* ("just felt") were found between experimental groups like in earlier reports (12, 5). It must be kept in mind, however, that estimation of sensation thresholds with the conventional graduated (stepwise) distension test is not very reliable. In addition, the pattern of (non-significant) group differences paralleled exactly that of pain thresholds: Thresholds of D and A groups were lower than those for H and C groups, which did not differ. This pattern may be suggestive when taken together with the (non-painful) *aversion threshold* ("slightly unpleasant"), for which highly significant differences in the expected direction were found ($D + A < H + C$: $p < 0.003$; t-Test. Consideration of *characteristic sensation curves* (probability of sensation as a function of distension volume and intraluminal pressure; cf. Figure 8) corroborates this interpretation: The same pattern of differences between pairs of subgroups ($D + A > H + C$) appears for both non-nociceptive sensations, "just felt" and "just unpleasant, not painful", as was obtained for pain sensations (Figure 10).

Further support for an *unspecific local* visceral hypersensitivity (to distension) comes from retrospective ratings which were obtained at the end of the distension test. When asked to rate their perceptions during the distensions series on a 4-point categorical scales ("not at all" to "strong"; "never" to "always"), $D + A$ groups rated significantly higher sensation intensities and frequencies in all sensation categories related to the lower abdominal tract, that is "balloon/distension felt" ($p < 0.0001$), "sense of pressure" ($p < 0.0001$), "pain" ($p < 0.0001$), and "urge to defecate" ($p < 0.05$). There was no rating difference in the category "sense of fullness" ($p = 0.322$, n.s.), which is related more to upper g.i.t.

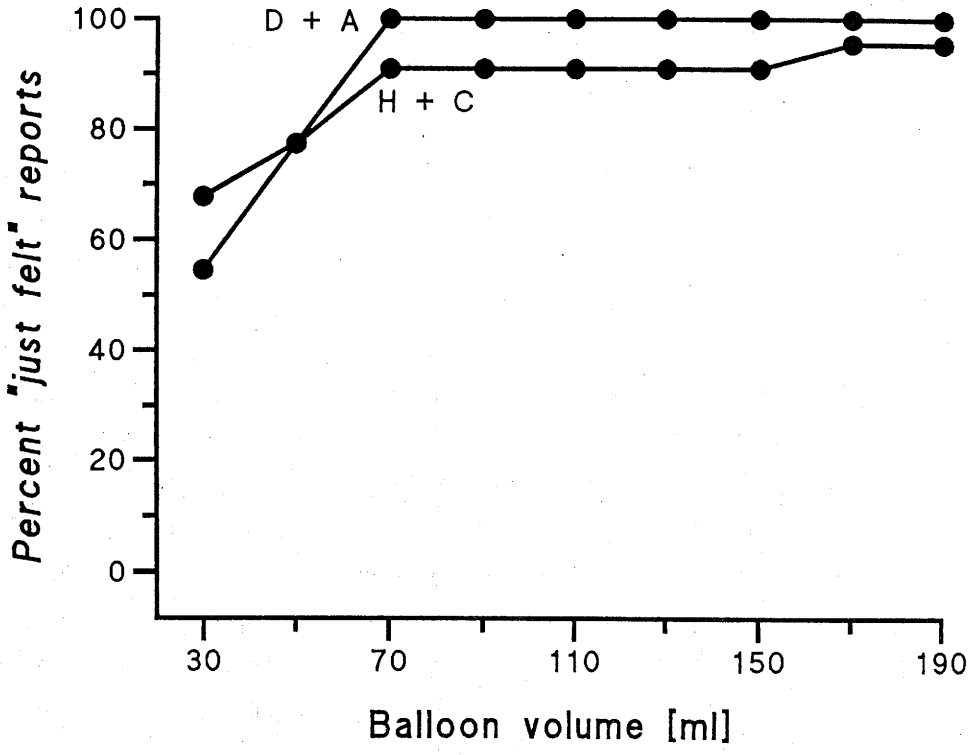
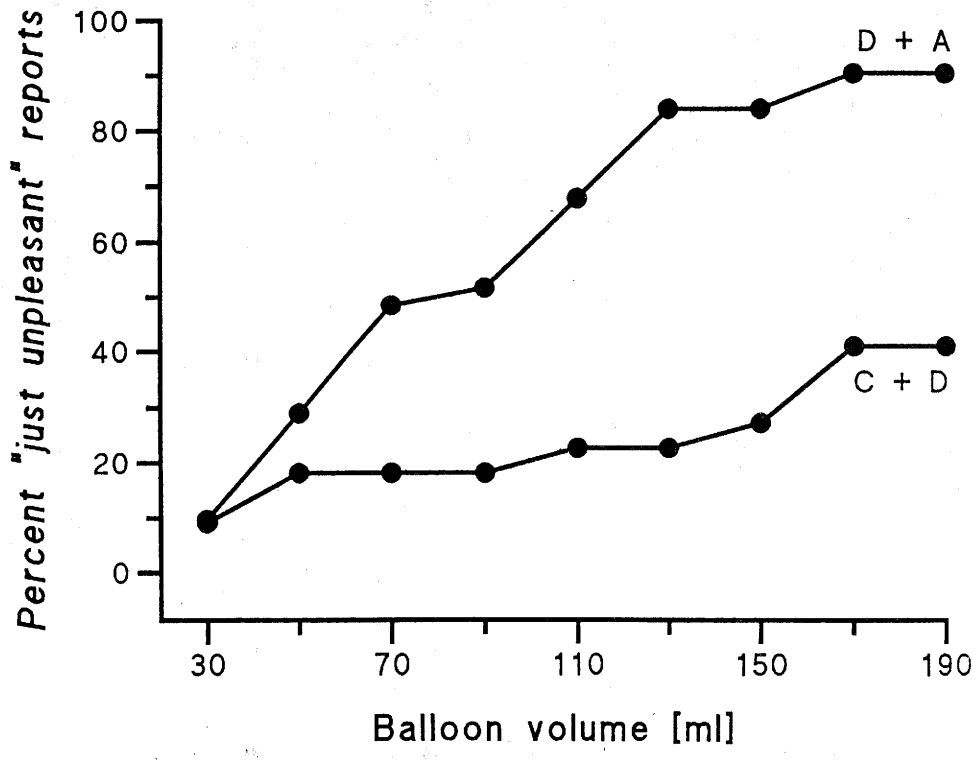


Figure 10: Psychophysical functions of non-nociceptive sensations.

a: Percentage of "just felt" reports in 2 IBS subgroups (D + A) compared to controls and constipated patients (H + C) as a function of balloon volume and pressure.



b: **Percentage of "just unpleasant" reports as a function of balloon volume and intraluminal pressure (corrected). (cf. Figure 8.)**

Cold pressor pain

Somatic pain sensitivity as measured by cold pressor thresholds (time until first pain report) and cold pressor tolerance (time until withdrawal) showed no significant differences between IBS patients and controls; if at all there was a slight tendency (n.s., Mann-Whitney U-tests) of IBS patients to *higher* tolerance. No differences between patient subgroups were found either. Subjective pain ratings are in accord with this finding (differences between IBS and controls and between subgroups n.s., Kruskal-Wallis test). This indicates that IBS patients are at least not more sensitive to somatic pain stimulation or pain in general, if not of higher pain tolerance as previous reports seem to indicate (see Introduction). This clearly contradicts a psychological explanation of reduced distension tolerance and is in accord with the main finding of the study, that the physiological basis of reduced distension tolerance is to be found mainly in lowered bowel compliance instead of heightened visceral pain sensitivity.

Skin temperatures at withdrawal support this interpretation additionally, because IBS patients do not withdraw at higher temperatures than controls, which they would if they had lower tolerance for cold pain. This could have reduced differences in insertion times by altered vasoconstrictor tone in IBS patients because it would alter cooling of the acra. However, there is a slight, but insignificant tendency of IBS patients to higher withdrawal values. Considering the fact that pain assessment by the Cold Pressor Test is not very precise and subject to various uncontrolled variables the issue seems not closed.

DISCUSSION

Different pain mechanisms in specific subgroups of IBS and the problem of diagnostic criteria

According to the results of this study, lowered bowel compliance as indicated by steeper pressure rises with increasing distension volumes explains lowered pain thresholds to *tonic* distension in IBS subgroups with diarrhea-predominant and alternating bowel symptoms. The study also showed that hypersensitivity to *phasic* distension as indicated by increased contractile activity elicited by the distension steps may also be explained by the compliance mechanism. Therefore it seems justified to conclude that a substantial part of the clinical symptomatology is due to lowered bowel compliance, although the study presents no direct evidence on the issue. Data from larger samples on the correlation between compliance test results and clinical symptomatology are needed.

For IBS-patients with diarrhea, then, altered peripheral transduction of distending stimuli through increased wall tension seems to be a parsimonious explanation of their pain symptoms. Changes in afferent information processing at higher stages, that is, in visceral pain perception per se, "instrumental" pain behavior etc., need not be assumed. In fact, there may be peripheral reasons of the tonic pressure response changes yet to be found. If, however, psychological factors are involved in altered visceral pain perception of diarrheic subgroups of IBS, they should to operate through changes in efferent commands controlling smooth muscle tonus or through tonic visceral reflex facilitation with its consequences on peripheral signal transduction rather than through changes in afferent signal transmission or processing.

A different, yet unknown mechanism must be responsible for the pain symptoms reported by predominantly constipated subjects. For instance, it could be related to spastic contractions in connection with passive overstretching of smooth muscles after longterm adaptation to large volumes (cf. 7). However, the present study does not allow to decide on this question. The slight trend for increased compliance in constipated subjects was not significant. To secure more definitive information on the question a different distension test with higher upper limits of end volumes would be required to separate constipated patients from controls. This was avoided in the present study for various reasons, one of them being ethical considerations and patient safety.

The finding that different visceral pain mechanisms seem to operate in diarrheic as compared to constipated subgroups shows that the visceral hyperalgesia found in the former cannot be related to the remaining psychopathometric characteristics in our IBS sample (cf. Table 1), because all three IBS subgroups shows this small increase in depressivity and trait anxiety. The finding shows also, that experimental analyses of pathophysiological and pathopsychophysiological mechanisms in functional bowel disorders in general require more specific group definition at least in terms of quality of clinical symptoms to reduce pathogenetic heterogenity. The practice of lumping together constipated patients in which compliance is not reduced (if not enhanced) with those patients in which compliance is reduced has confused the literature on visceral hypersensitivity and hyperalgesia in IBS.

In addition, it is possible and, in fact, not improbable that clinical characteristics alone are not sufficient to create pathophysiologically homogeneous subgroups for more principal reasons,

which have been discussed in the Introduction. Therefore, further sophistication of diagnostic criteria based on symptomatology alone would only lead to "building castles in the air" (6) instead of defining units of disease. Reliable and valid functional tests like the one elaborated for the present study must be added to supplement clinical criteria with independent laboratory information on the existence of a particular functional aberration like lowered compliance etc. This is exemplified even in this study, in which, although highly significant differences between clinical subgroups were found, a certain percentage with normal compliance was still found in the diarrheic groups. This may not be neglected under a diagnostic perspective (see Results on discriminative specificity). This is particular important if therapeutic measures are to be concluded from identified compliance changes. Studies, which try to provide the empirical basis for the differential indication of specific compliance treatment in this way, are currently undertaken in several laboratories including ours (8, 53).

Because lowered bowel compliance is a local pathophysiological mechanism (myogenic or enteric neuronal) under possible central neuronal and humoral control, but no disease, this relation between clinical groups and the visceral hyperalgesia of IBS patients is not really surprising. It points also to the acknowledged fact that the syndrome reflects no single disease unity. However, most group studies in the field were and many still are designed according to an implicit "disease" concept of IBS. This is also demonstrated by the relative weight which has been laid on refinement of criteria for clinical diagnosis compared to further basic studies on psycho-pathophysiological mechanism. It is suggested that Ritchie's promising attempt to explain IBS pain symptoms by altered bowel compliance initially was not successful and abandoned prematurely, because he adhered to this misconception of pathophysiological homogeneity of the syndrome which led him to neglect possible differences in mechanism between symptomatic or otherwise defined subgroups and within subgroups in the selection of his experimental groups (1-3, 7).

Group selection by clinical criteria can serve as a first homogenisation of the syndrome in this approach, but identification of specific pathophysiologic mechanisms for particular symptoms and subsequent narrowing to subsyndromes by presence of pathophysiologic markers like particular motility changes, or visceral hypersensitivity must follow. It is suggested that the conflicting picture of motility findings in IBS may be resolved in a similar way.

As far as assessment of visceral sensitivity is concerned, expansion of test paradigms including non-nociceptive visceral thresholds like absolute distension threshold, location discrimination thresholds and others with higher precision than the compliance test used in the present and similar studies is very much needed to improve our understanding of visceroceptive pathology in functional gastrointestinal disorders and devise clinical applications of it. It is an established fact that non-painful discomfort symptoms like bloating, upper abdominal "pressure" feelings etc. have a large intero- ceptive component in addition to the "objective" changes (gas, dysmotility, reflux) to which they are usually attributed. Further elaboration of interoceptive test tools, therefore, is an important methodological aim in the field. Work in this direction has been reported by several laboratories, but results seem not yet applicable on a broader basis or even clinically (41, 54). The reason seems to ly again in technical limitations as earlier in the field of

compliance. It can be expected from the preliminary reports available that these limitations will be overcome within the next few years.

Transduction models and central control of visceral sensitivity

Compliance and visceral tonus. As discussed, reduced bowel compliance may be interpreted as the consequence of increased bowel tonus, if mechanical changes in wall stiffness as a result of scleroderma etc. are ruled out. However, usually no differences in basal resting pressure in IBS patients are found (12 etc. and in this study). Therefore, enduring tonic contraction of bowel muscles under basal conditions cannot be the crucial factor. But, according to a simple model of force transduction in the bowel wall (40, 55 cf. 56), lowered bowel compliance may also be explained by increased tonic reflex activity in response to distension. This results in a steeper pressure-volume characteristic. In fact, compliance is measured by its slope, $\Delta p/\Delta V$, the ratio of pressure change (= bowel response) to volume change.

As this study shows, genuine hypersensitivity of enteroceptors or afferent systems is not required to explain apparent hypersensitivity in those groups where lowered compliance could be demonstrated: It results in steeper pressure rises with given volume increases and, therefore, earlier suprathreshold stimulation of visceral nociceptors (as referred to volume) without hypersensitivity of enteroceptors to stretch (force or pressure). In fact, *higher* pressure tolerance was found in patients with *lowered* volume tolerance.

In as much as visceral reflex tonus or excitability depends not only on local (myogenic, entero-neuronal or humoral) variables, but is also under control of autonomic innervation, compliance changes may be caused also by efferent signals to the bowel, and finally, by psychophysiological mechanisms mediating between psychological factors (affect, "stress" etc.) and autonomic activity. While "stress" effects on contractile activity and transit have received much attention in the literature since the Forties (57, 58, 59, 60, 61, cf. 26, 62), central effects on bowel tonus have been largely overlooked as possible mediators between brain and gut, because they do not show as direct efferent consequences on motility, but only indirectly as changes in sensitivity to intraluminal stimuli. The compliance mechanism offers a parsimonious explanation of such changes in functional or "psychosomatic" disorders of the gastrointestinal tract (63).

The peripheral model implies a physiological mechanism operating not only under pathological conditions and at nociceptive stimulus levels. In addition, there is good evidence that visceral nociception does not involve special high threshold receptors as supposed by the "specificity theory" of pain but is encoded by the same low threshold receptor population as non-nociceptive sensations from the viscera (52,30). Therefore, it should be possible to test the mechanism in healthy subjects at non-painful stimulus volumes, in particular, also near perception thresholds. This was tested in two subsequent analogue studies with healthy subjects reported elsewhere. Preliminary results indicated that perception thresholds for phasic distension stimuli in the colon are indeed dependent on wall tension (64, 63, 40). It remains to be shown, whether these preliminary data can be replicated and extended to perception thresholds in IBS subpopulations as well.

Tonus, phasic distensions, and active contractions. Considering central influences on bowel compliance is particularly relevant in view of the findings of the present study, that the tonic parameter bowel compliance not only determines apparent sensitivity to *tonic* distension but also to *phasic* stimuli, and that differences in visceral reflex responses to them are fully accounted for by the differences in tonic properties, that is compliance characteristics. A closer look at the transduction situation shows that this relation depends not necessarily on correlations between tonic and phasic visceral reflex excitability, but that there are already simple biomechanical reasons: The steeper pressure-volume characteristic with lowered compliance increases not only tonic but also phasic pressure changes to phasic distension on the same simple physical grounds, thereby causing higher stimulation increments and lowering the threshold for phasic stimuli which stem from passage of stool/gas or active contractions without any genuine hypersensitivity (65, 40). This is also relevant for the pathophysiological role of large contractions in connection with mass movements, which have been related to clinical pain symptoms in some patients (27).

In as much as primary and secondary reflex responses to phasic and tonic distension depend on compliance it is also to be considered as a variable which moderates motility differences of IBS patients compared to controls. The instability of motility findings in IBS may indicate that motility changes - at least in subgroups with altered compliance - are no primary pathophysiological variable at all but the secondary consequence of lowered compliance. It seems mandatory, therefore, to simultaneously assess compliance in studies trying to identify motility aberrations (cf. 4).

Compliance changes in other disorders

Non-cardiac chest pain and functional dyspepsia. The discussion of visceral pain mechanisms and compliance effects on overall visceral sensitivity is not limited to IBS. Similar arguments hold for the pathophysiological analysis of functional disorders in other segments of the gastrointestinal tract, in particular, the syndrom of non-cardiac chestpain which received much attention during the last decade (cf. 66/review). Although in this case available data seem to support a genuine hypersensitivity explanation (67), the issue is not settled and differing subgroups might be identified as in the present study on IBS provided that adequate measurement techniques and study designs are used. In any case, the finding of the present study, that visceral hypersensitivity in functional disorders of the gas-trointestinal system may be due to reduced compliance rather than afferent hypersensitivity proper, is not specific to IBS or, even to the particular population investigated here: Bradette and his co-workers have shown in a recent study that patients suffering from „functional dyspepsia„ show increased sensitivity to gastric distension, but corresponding pressure changes were not enhanced compared to controls (68). Because of somewhat different methods compliance measures were not obtained, however, so that the results are conclusive in respect to the mechanism discussed here. Obviously, direct compliance assessment and differentiated analysis of the mechanism of gastric hypersensitivity in these patients is needed. The strategy used in the present study would seem to be suitable for this purpose.

Autonomic Diabetes Neuropathy. How complicated the interrelations between local compliance changes and afferent changes may be is clearly exemplified by findings on gastrointestinal, particularly, rectal and rectosigmoidal sensibility changes in diabetes patients. It is usually assumed that heightened thresholds to distension in these patients result from neuropathic deafferentation (69 etc.). However, changes of smooth muscle tone (usually reductions) and heightened compliance may also be present at the same time (70). In that case, stimulus transduction is greatly impaired and secondary sensitivity changes may appear without deafferentation signs. Here again, therefore, compliance assessment concomitant with sensitivity evaluation is necessary. This holds whether subjective thresholds or evoked potentials are used. The contradicting findings in this area may be the result of the insufficient control of the biomechanical conditions during stimulation which characterizes most studies on the subject (71).

The preliminary report by Sarno et al. (70) on compliance and sensitivity changes in Diabetes patients with autonomic neuropathy contains another feature which is relevant to the IBS discussion: In a subgroup of Diabetes patients, that is, a group with diabetic diarrhea, visceral hypersensitivity instead of the expected hyposensitivity was found. However, the combination of visceral hypersensitivity and predominant diarrheic g.i. symptoms was *not* accompanied by lowered compliance! That means, that assuming a constant relation between a particular combination of bowel symptoms (e.g. diarrhea and pain) and the finding of lowered compliance in the subgroup showing them does not exist and may not be generalized across disorders. It may well be that the clear picture of compliance effects on sensitivity and g.i. symptoms found in the present study will be blurred again by analoguous complications when a closer look is taken at the broader class of functional bowel disorders and/or other populations.

CONCLUSIONS

1. Experimental and theoretical analysis of the factors involved in apparent visceral hyperalgesia associated with IBS accentuates the necessity of careful *subgroup definitions* in identifying specific pathophysiological or patho-psychophysiological mechanisms which can be related to clinical symptomatology, especially to the nature of the supposed "irritability" in the irritable bowel (cf. 72, 73).

2. Classification by more sophisticated clinical criteria may be helpful but not always effective in regard to pathophysiological homogeneity. For mechanism-oriented research as well as for the development of more specific treatments, independent assessment by use of *pathophysiological and/or patho-psychophysiological markers* derived from *standardized function tests* is required. The compliance test as it emerged from converging studies during the last decade presents a methodologically sound and pathophysiologically relevant example.

3. Further development of visceral sensitivity tests is needed to cover the full range of stimulus intensities from sensation threshold to thresholds for discomfort and pain. Such a set of tests allows to characterize comprehensively the changes in generation and processing of afferent signals from the gastrointestinal tract which are supposed to be at the root of clinical symptoms and subjective complaints in functional g.i. disorders and related syndromes. This demands not only sufficient specification of the biomechanics of stimulus transduction as attempted for tonic distension in this study, but also more general visceral sensitivity tests which meet the methodological standards required in other area of (exteroceptive) psychophysics. Promising candidates for this purpose have been developed in psychophysiological studies on interoception (41).

4. The approach of experimental psychophysiology to functional disorders of the g.i.t. with its emphasis on model-oriented versus disease-oriented investigation is also of practical relevance in differential diagnosis of g.i. disorders: Its application in quantitative psychophysics of visceral pain and interoception, especially the methods of assessing local transduction characteristics and afferent visceral signal detection *in the intact human subject* may be used clinically to differentiate visceral pain syndromes on the basis of their patho-psychophysiological mechanisms. In this way, it may be hoped that it will eventually be possible to separate the varying contributions of peripheral and central factors in individual patients suffering from gastrointestinal pain syndromes.

ACKNOWLEDGEMENTS

This research was jointly supported by the German Research Council (Deutsche Forschungsgemeinschaft, DFG) by grants to the senior author (contracts Ho 904/3-1ff.) and the Max-Planck-Gesellschaft (MPG). The empirical part of the study was completed while the authors were still at the Max-Planck-Institute for Psychiatry, Munich. Administrative support by the City Health Authorities, Munich, the most valuable assistence of Dr. Höchter (City Hospital München-Neuperlach) in the patient recruitment and screening as well as in the definition of inclusion and exclusion criteria for IBS are gratefully acknowledged. The project was part of a collaboration with Prof. W. E. Whitehead (University of North Carolina, Chapel Hill). Most of the ideas put forward stem from many discussions, sometimes controversial, with him and his coworkers at his former Laboratory at John Hopkins, Baltimore. Ample reference to this source is made in the text, but its actual contribution goes a lot further. This is acknowledged by including him as co-author. Finally I want to thank Marian Cebulla for his support. Without his exceptional work supply this manuscript could not have been sent to the editor.

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List of Abbreviations

A:	Alternating bowel symptoms
ANOVA:	ANalysis Of VAriance
BDI:	Beck's Depression Inventory
C:	Constipation-predominant bowel symptoms
CI:	Compliance Index, CI = $\Delta p/\Delta V$ [hPa/ml]
D:	Diarrhea-predominant bowel symptoms
DF:	Linear discriminant function
Δp:	pressure difference [hPa, 1 hPa = 1 mbar = 1 cm H_2O = 0,74 mmHg]
ΔV:	Volume difference
FBD:	Functional Bowel Disorder (Drossman et al., 1990, 16)
GDT:	Graduated Distension Test
H:	Healthy control subjects
IBS:	Irritable Bowel Syndrome
ICS:	Irritable Colon Syndrome
MI:	Motility Index
P_{sr}:	Subjective pain-rating
PA:	Pump artifact
PC:	Primary contractions
PCA:	Amplitude of primary contraction
PCM:	Pulse Coded Modulation
RF:	Regression function
SC:	Secondary contractions
SCA:	Amplitude of secondary contractions
SCA_{max}:	Amplitude of maximal secondary contraction
SCI:	Secondary contraction index
$t_{cp.0}$:	Time until first pain sensation after immersion of the hand into the icewater
$t_{cp.w}$:	Time until hand withdrawal after immersion of the hand into the icewater
T_w:	Skin temperature at withdrawal
VT:	Volume threshold