INAUGURAL MEETING OF THE NEUROGASTROENTEROLOGY AND MOTILITY SECTION OF THE BRITISH SOCIETY OF GASTROENTEROLOGY

PROGRAMME AND ABSTRACTS

7th SEPTEMBER 2001

ROBINSON COLLEGE, CAMBRIDGE
Dear Colleague

On behalf of the Neurogastroenterology and Motility Section of the BSG, we are pleased to be able to welcome you to Robinson College. Considerable effort has been extended over the last year in creating the new Neurogastroenterology and Motility Section, which is vital if we are to improve awareness and understanding in this area of Gastroenterology. The importance of section status lies in the fact that we now have a direct input into the BSG annual programme, which has in the past neglected functional GI diseases. The present meeting has been generously supported by Novartis who have given the committee a free hand in arranging what, I hope you will agree, is an attractive programme. We look forward to some fascinating presentations and hope that you will add to the value by actively participating with comments and questions at the end of each session.

Best wishes

[Signature]

Professor Robin Spiller
Chairman
Neurogastroenterology and Motility Section
British Society of Gastroenterology
PROGRAMME

Appetite, Nausea and Vomiting

How does the brain know how much the animal should eat?  
Gareth Williams, Liverpool  9:00

Pathophysiology of nausea  
David Grundy, Sheffield  9:35

Upper GI motility evaluation in NUD – does it help?  
André Smout, Utrecht  10:10

Coffee/Tea  10:45

Emotions and the Gut

Stress and gastrointestinal motility  
Hubert Mönnikes, Berlin  11:15

Emotional and cognitive modulation of gut feelings  
Qazim Aziz, Manchester  11:50

Lunch  12:25

Is There Science Behind Bloating?

Measuring bloating and its clinical significance  
Peter Whorwell, Manchester  13:30

How the gut handles gas in IBS: implications for treatment  
Eamonn Quigley, Cork  14:05

Food intolerance and the irritable bowel syndrome  
John Hunter, Cambridge  14:40

Coffee/Tea  15:15

Evolving areas in IBS

Mucosal associated bacteria in IBS: their relevance for treatment?  
Louis Akkermans, Utrecht  15:45

5HT and IBS  
Lesley Houghton, Manchester  16:20

Close  17:00
Professor Louis Akkermans  
*Professor in Gastrointestinal Physiology*  
*Utrecht University Hospital, Netherlands*

Louis Akkermans received his undergraduate training in Biology at the Utrecht University in The Netherlands. Then he pursued graduate studies also at the Utrecht University and received his Ph.D. degree in 1974. His thesis was on an electrophysiological investigation on the mode of action of the insecticide dieldrin. He pursued a post-doctoral specialization in pharmacology. His research in animal and human gastrointestinal motility started in 1975. He was appointed as a senior lecturer and Head of the Experimental Surgery Department in Utrecht. In 1987 he was appointed as a part-time Professor of Neuro-physiology at the University of Wageningen. In 1992 he was appointed as a full time Professor in Gastrointestinal Physiology at the Department of Surgery and the Gastrointestinal Research Unit at the Utrecht University and the University Medical Center Utrecht. He is a co-chairmen of the Gastrointestinal Motility Laboratory. Part of his research is performed in the Rudolf Magnus Institute for Neurosciences. He is currently the Executive Chairmen of the European Society of Neurogastroenterology and Motility, is a member of the management committee of the journal of the society, Neurogastroenterology and Motility. He is a member of the Scientific Committee of the European United Gastroenterology Federation (UEGF).

His present research is focused on: Pathophysiological studies in gastrointestinal motility; CNS and peripheral mechanisms for sensitization of the brain-gut axis; gastrointestinal motility, small bowel bacterial overgrowth, and bacterial translocation; gastrointestinal motility disturbances and the autonomic nervous system. His non-GI research interests include LF/HF heart rate variability, MSNA (Muscle Sympathetic Nerve Activity) and cerebral blood flow investigations into the pathophysiology of postprandial hypotention.

Dr Qasim Aziz  
*Senior Lecturer and Honorary Consultant Gastroenterologist*  
*Hope Hospital, Salford, UK*

Following his initial clinical training in Pakistan, Dr Aziz trained in General Medicine and Gastroenterology in the UK. Since 1991, he has been consistently involved in research and is currently a Medical Research Council Clinician Scientist. His major research interest is to study the human brain gut axis using functional brain imaging techniques. His Ph.D. research led to the identification of the human brain swallowing centres and demonstrated that they were represented asymmetrically, and damage to the dominant hemisphere for swallowing control, for instance by stroke, led to the development of dysphagia.

His worked has also contributed to the current understanding of the brain neural networks involved in processing human gut sensation. He is currently studying factors that modulate the brain processing of gut sensation in health and in patients with functional gastrointestinal disorders.
**Professor David Grundy**  
*Professor of Biomedical Science  
University of Sheffield, UK*

Having graduated in Physiology from Queen Elizabeth College, University of London in 1975, Professor Grundy migrated north to the University of Dundee to take up a postgraduate scholarship to study vagal mechanism controlling gut function with Joe Davison. He moved to Sheffield in 1978, as a research fellow with Tim Scratcherd, and was appointed as lecturer in 1980. In 1987 he was awarded a prestigious Wellcome senior fellowship and appointed to a personal chair in 1999.

He has approached the study of gastrointestinal regulatory mechanisms from a neurophysiological standpoint and is best known for his work on visceral sensory mechanisms. He was awarded the Janssen award for Basic Research in the Digestive Sciences in 1999. He is currently editor of "Neurogastroenterology and Motility", guest professor in the Surgery department at the University of Tübingen and a member of the scientific council of the Pavlov Institute in St Petersburg.

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**Dr Lesley A Houghton**  
*Non-clinical Senior Lecturer in Medicine and Physiological Sciences  
University of Manchester, UK*

Dr Houghton is Manager of the Gastrointestinal Physiological Services for South Manchester University Hospitals NHS Trust, U.K. Following an undergraduate degree in Biochemistry and Physiology and a PhD on the relationship between gastric emptying and antro-pyloro-duodenal motility in man at the University of Sheffield, she spent a year as a research fellow at the Royal Adelaide Hospital, South Australia after which she returned to the University of Sheffield. Since 1989 she has directed the physiological research programme at the Department of Gastroenterology, University Hospital of South Manchester.

Dr Houghton’s current research interests include the role of 5-hydroxytryptamine (5-HT) and receptors 5-HT1, 5-HT3 and 5-HT4 in the control of GI function, GI motility disorders, and functional bowel disorders with particular reference to the aetiology of abdominal bloating in patients with irritable bowel syndrome, the effects of gender and psychological/ environmental stressors on GI function and the mechanisms of action of hypnotherapy in its efficacy of treatment of these disorders. As well as being principal investigator in a number of physiological studies of new pharmacological agents for the treatment of functional bowel disorders, Dr Houghton has given numerous research presentations at national and international meetings. She is the co-editor of a book on IBS and author/co-author of over 60 original publications, book chapters, reviews and other articles.
Dr John Hunter
Consultant Physician and Director of Gastroenterology
Addenbrooke’s Hospital, Cambridge.

Dr Hunter has published many research papers in gastroenterology, especially irritable bowel syndrome and inflammatory bowel disease. He has pioneered the use of diet in the management of IBS leading to the development of a rational understanding of this condition. This has led to the realisation that abnormal fermentation by the gut flora is an important factor in the pathogenesis of disease which was previously unrecognised, and which may have wide importance in human health.

Professor Hubert Mönnikes
Associate Professor of Medicine and Assistant Medical Director,
Department of Medicine,
Universitätsklinikum Charité, Humboldt University, Berlin, Germany

Prof Mönnikes is the Head of the Neurogastroenterology and Motility Research Unit of the Universitätsklinikum Charité at the Humboldt University in Berlin. His research interests are neuro-gastroenterology and gastrointestinal motility, gastrointestinal hormones and neuropeptides, mechanisms of brain-gut interaction, functional gastrointestinal disorders and visceral pain. In addition, Prof Mönnikes has a key interest in psychophysiology, psychosomatic, psychotherapy stress and gastrointestinal function.

Professor Eamonn M M Quigley
Professor of Medicine and Human Physiology and Head of the Medical School
National University of Ireland, Cork.

Following medical training at the National University of Ireland in Cork and junior posts in Cork and Glasgow, Professor Quigley spent two years at the Mayo Clinic, followed by two years at the University of Manchester in Salford. After this, he returned to the States as Assistant Professor at the University of Nebraska Medical Center in Omaha. He was the Chief of Gastroenterology at UNMC from 1991-1998 and was awarded full professorship in 1998.

As well as his current roles in Cork, Professor Quigley maintains his US links as an Adjunct Professor of Medicine and Physiology at the University of Nebraska. He has published widely, mostly on gastrointestinal motility and functional gastrointestinal disorders, and has over 400 original articles, reviews, editorials and book chapters to his name. Professor Quigley is both Editor-in-Chief of the American Journal of Gastroenterology and Secretary-General of the Organisation Mondiale de Gastroenterologie.
**Professor André Smout**  
*Consultant Gastroenterologist*  
*Utrecht University Hospital, Netherlands*

Having studied medicine at the University of Amsterdam, Prof. Smout subsequently specialized in Internal Medicine and Gastroenterology in Rotterdam and Utrecht. Since 1984, he has been working as a gastroenterologist at the Utrecht University Hospital.

Since 1976 Prof. Smout's research activities have been devoted to gastrointestinal motility. His thesis on the myoelectrical activity of the stomach was published in 1980. His major research topics are: gastro-oesophageal reflux disease, noncardiac chest pain, functional dyspepsia, irritable bowel syndrome, 24-hour ambulatory monitoring of oesophageal, gastric and small intestinal motility, and the clinical application of electrogastrography.

In 1994 Prof. Smout became holder of the extraordinary Chair "Pathophysiology and clinical implications of gastrointestinal motility", instituted by the Dutch Digestive Disease Foundation. Prof. Smout is author of about 150 scientific publications and several books on gastrointestinal motility.

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**Dr Peter Whorwell**  
*Director, Functional Gastrointestinal Service, University Hospital of South Manchester, Manchester, UK*

Dr Peter Whorwell graduated in medicine from Guy’s Hospital, UK, in 1969. After completing his initial studies he went on to complete further training at Addenbrooke’s Hospital, the Hammersmith Hospital, the Royal Brompton Hospital, and Westminster Hospital. Dr Whorwell later undertook a fellowship in gastroenterology at the University of Vermont, USA.

In 1981, Dr Whorwell returned to the UK to take up a position as Gastroenterologist and Senior Lecturer at the University Hospital of South Manchester. Dr Whorwell is the author/co-author of more than 150 scientific publications. His research interests focus on functional GI disorders and their treatment.

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**Professor Gareth Williams**  
*Professor of Medicine and Director of the Diabetes and Endocrinology Research Group*  
*University Hospital Aintree, Liverpool*

Qualifying in medicine with Honours from Cambridge in 1977, Gareth Williams did junior posts in London and Geneva and following a clinical MD on brittle diabetes with John Pickup and Harry Keen (Guy’s Hospital, London), he worked with Stephen Bloom (Hammersmith Hospital) and there developed an interest in regulatory peptides.

His research group's interests span a broad spectrum from the role of hypothalamic peptides in energy homeostasis, to the clinical management of diabetes and obesity. He is co-editor of the Textbook of Diabetes, whose second edition won the BMA Book of the Year award, and was UK President of the Anglo-French Medical Society from 1993-2000.
HOW DOES THE BRAIN KNOW HOW MUCH THE ANIMAL SHOULD EAT?

Gareth Williams
University of Liverpool, UK

The hypothalamus regulates overall energy homeostasis and can respond to a wide range of neural and humoral signals that control feeding behaviour. It is now clear that certain hypothalamic pathways serve specific functions under particular conditions. Some of these will be described to illustrate the complexity of these systems and their interactions.

Neuropeptide Y (NPY), expressed by neurones in the arcuate nucleus (ARC), is a powerful inducer of hyperphagia and obesity. The ARC NPY neurones are normally inhibited by leptin and insulin and are overactive in starvation, when circulating levels of these hormones fall. The ARC NPY neurones may therefore function particularly to defend body weight against severe energy deficits.

Activation of the melanocortin-4 receptor (MC4-R) inhibits feeding and causes weight loss, and may be involved in limiting overeating and obesity in rats given palatable food. The endogenous ligand at the MC4-R is thought to be a-MSH, a cleavage product of pro-opiomelanocortin, which is produced by other neurones of the ARC. MC4-R activity is also modulated by release of agouti gene related peptide (AGRP), an endogenous inhibitor of the MC4-R, which is released by the ARC NPY neurones.

Orexins A and B are expressed in specific neurones of the lateral hypothalamus (LHA) that have extensive reciprocal connections with many appetite-regulating brain regions, including the nucleus of the solitary tract which relays vagally-transmitted satiety signals from the viscera to the LHA. Orexin A stimulates feeding acutely and orexin neurones are activated by falling glucose but promptly inhibited by feeding, suggesting a role in ‘on-off’ feeding episodes and in hypoglycaemia-induced hyperphagia.

Unravelling the roles of individual neuronal pathways will be difficult, but is an essential step in the rational development of drugs to treat obesity and other nutritional disorders.

References:
Hypothalamic peptides and feeding

**Hyperphagia**
- NPY
- AGRP
- MCH
- Orexin A
- Galanin

**Hypophagia**
- α-MSH
- β-MSH
- CRF
- CART
- CCK
- GLP-1
- ETC

NPY/AGRP and POMC cells in feeding

NPY → Y3 → Increased feeding
AGRP → ?? → Decreased feeding
MSH → MC4-R: tonic restraint?

NPY/Y5: counters starvation?
AGRP/β3: SDR

Human obesity: not due to absolute leptin deficiency

Relative leptin deficiency? Leptin resistance?

Human obesity: rare genetic causes

- POMC (recessive)
- PC-1 (recessive)
- MC4-R (dominant)

Leptin receptor (recessive)

Leptin (recessive)

Fat

Reduced hunger
PATHOPHYSIOLOGY OF NAUSEA

David Grundy
The University of Sheffield, UK

The gastrointestinal tract is involved in triggering nausea and vomiting. It also contributes to the expression of nausea through alterations in motor activity that return intestinal contents to the stomach prior to their expulsion brought about by contractions of the diaphragm and abdominal muscles. These gastrointestinal events have been implicated in the genesis of nausea but current opinion suggests that these are epiphenomenon. However, there is strong evidence that 5-hydroxytryptamine, released from enterochromaffin cells, is a powerful emetic trigger that functions as part of a luminal toxin-detection mechanisms. 5-HT released from the gut mucosa acts on the sensory terminals of vagal afferent fibres that relay to the brainstem circuits that orchestrate the emetic response. Radiation and cancer chemotherapy agents cause nausea and vomiting via this mechanism but the development of 5-HT3 receptor antagonists has profoundly affected the incidence of these side effects of anti-cancer therapy, particularly in the acute phase of treatment. These agents are also proving effective in the treatment of post-operative nausea and vomiting.
**Toxin Detection in the GI tract**
- 5-HT released from the GI tract is a peripheral trigger for emesis
- Vagal afferents convey the emetic trigger
- Part of a defense mechanism to protect against ingested pathogens.

**GI motor correlates of nausea**
- Exhalation caused by contractions of the crural diaphragm and abdominal wall
- The proximal stomach relaxes to accommodate retching intestinal contents
- Antral motility inhibited to prevent gastric emptying
- Retrograde Giant Contractions return intestinal contents to the stomach

**Emetic response to anticancer chemotherapy**
- Intensity of emesis
- Cisplatin
- Anthracyclines
- Delayed
UPPER GI MOTILITY EVALUATION IN NUD – DOES IT HELP?

André Smout
University Medical Centre, Utrecht, The Netherlands

Non-ulcer (or functional) dyspepsia (NUD) is a label given to patients complaining of upper abdominal discomfort or pain, nausea, early satiety and related symptoms when appropriate investigation fails to bring organic pathology to light (1).

There is no doubt that NUD is a hotchpotch of abnormalities rather than a well-defined homogeneous disorder. Several decades of research have made clear that disordered upper GI motility and hyperperception are important pathophysiological factors. Recent observations suggest that hypersensitivity to duodenal acidification plays a role in a subset of patients with NUD (2). The role of psychological factors in NUD remains difficult to assess.

Whereas many techniques for assessment of gastrointestinal motility have been used in scientific studies in NUD (Figure 1), only a few of these have found their way to daily clinical practice. This may be indicative of the fact that clinicians are not impressed by what motility evaluation has to offer to doctor and patient, but may also reflect the fact that many of the tests are too cumbersome or expensive to be applied on a routine basis.

The test that is probably used most often in the evaluation of NUD is measurement of gastric emptying. The rationale for this test is, firstly, that delayed gastric emptying is a common finding in NUD. On average, gastric emptying is delayed in 37% of dyspeptics (figure 2) (3). Secondly, prokinetic drugs relieve dyspeptic symptoms better than placebo (4). Ideally, emptying of both the solid and the liquid component of a meal are measured, using a double-isotope technique. Scintigraphy allows one not only to assess the rate of gastric emptying, but also to determine whether abnormal intragastric distribution of the meal is present (5). However, the limited availability of scintigraphic facilities and its high cost dictate that in the vast majority of cases, a short trial with a prokinetic drug will be preferred over measurement of gastric emptying. This may change when C13-octanoic acid breath tests become more widely available as a technique for measurement of gastric emptying.

Ultrasonographic measurement of antral diameter or antral area is technically simple. The antrum is wider in NUD than in health and cisapride reduces the antral area (6), but the specificity and sensitivity of this abnormality for NUD has not been determined. The decrease of antral area in the postprandial phase has been shown to be related to gastric emptying, but this does not make measurement of antral area a reliable technique to measure gastric emptying.

Manometry of antrum, duodenum and proximal jejunum is felt to be useful in selected cases of NUD, not because NUD is associated with specific motor abnormalities (Figure 3) but because manometry may help to differentiate NUD from chronic idiopathic intestinal pseudoobstruction (CIIP). For this purpose recording in the fasting state is far more relevant than postprandial recording since most of the characteristic abnormalities in CIIP are seen in the interdigestive state (abnormal interdigestive motor complexes).

Electrogastrography (EGG) is becoming increasingly popular as a screening test in NUD. This is largely a consequence of the commercial availability and the simplicity of the test. It has been shown that patients with NUD, as a group, have a smaller increase in the amplitude of 3-cpm activity after a meal and a higher percentage of electrical activity with abnormally high frequency (tachygastria) (7,8). Both abnormalities can be detected with electrogastrography. However, there are several problems associated with widespread application of EGG. Firstly, it is still not completely clear what is being measured with EGG. Secondly, automated analysis of EGG signals using Fast Fourier Transform can lead to spurious peaks in the frequency (or power) spectrum (9). Thirdly, commercially available software for EGG analysis uses criteria for "tachygastria" and "bradygastria" that easily lead to overdiagnosis of these conditions. Users of the technique who are relying on the outcome of fully automated analysis may thus contribute to the "gastric dysrhythmia epidemic" that is spreading over the world.
Impaired proximal gastric accommodation to a meal is an abnormality that can be found in substantial proportion of patients with NUD (10, 11). This abnormality can be demonstrated with barostat technology. However, swallowing the barostat catheter with the attached bag is not a procedure that is readily accepted by the average NUD patient. In addition, drugs that specifically promote relaxation of the gastric fundus are not yet available. Impaired accommodation of the proximal stomach can also be tested with three-dimensional ultrasonography. The latter technique requires considerable expertise and special equipment and is thus unlikely to become a widespread technique.

The electronic barostat can also be used to assess perception of gastric distension. It has been shown that visceral hyperperception is present in about 50% of NUD patients (12) and this abnormality undoubtedly plays an important role in the pathophysiology of NUD. Again, it is unlikely that barostat assessment of gastric perception will soon become a popular diagnostic tool. This might change when drugs become available that selectively reduce visceral hyperperception.

The waterload test (13) is an attempt to measure gastric accommodation without invasive and expensive equipment (“the poor man's gastric barostat”). The test has several disadvantages. First, the amount of water that can be drunk is not only determined by the accommodation of the stomach but also by the rate of gastric emptying. Secondly, the patient is not blinded to the procedure. Thirdly, it does not seem to be very helpful when a patient seeking medical advice for the symptom of early satiety, demonstrates in the lab that he or she has early satiety.

In conclusion, the heterogeneous and incompletely elucidated pathophysiology of NUD precludes a single diagnostic test for this condition and most patients with NUD are empirically treated without motility evaluation. Measurement of gastric emptying is usually considered to be the most helpful test; in patients who have delayed gastric emptying, treatment with prokinetic agents should be pursued more stringently than in those with normal emptying. Antroduodenojunal manometry should be done in cases of severe dyspepsia in which there is suspicion of chronic idiopathic pseudoobstruction. Tests for visceral hypersensitivity are not yet helpful, firstly because they are either too invasive or too little informative and secondly because drugs that specifically decrease visceral perception are not yet available.

References:


Upper GI motility tests in NUD

- **gastric emptying tests**
  - radionuclide: ++
  - C13 breath test: ++
- **antrioduodenal manometry**: +
- **electrogastrography**: ++
- **ultrasound measurement of antrum**: ++
- **water load test**: +
- **barocap measurement of**
  - perception of gastric distension: -
  - postprandial gastric relaxation: -
- **3-D ultrasound of stomach**: ++

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**Gastric emptying of solids in functional dyspepsia**

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36.7%
STRESS AND GASTROINTESTINAL MOTILITY

Professor Hubert Mönnikes
Universitätsklinikum Charité, Humboldt-Universität zu Berlin, Germany

CENTRAL CIRCUITRY OF STRESS RESPONSE: In recent years an evolving understanding of mechanisms underlying brain-gut interactions, particularly under conditions of acute and chronic stress, has enabled considerable progress in the understanding of the biological mechanisms by which psychological factors, like exteroceptive stress, translate into physiological responses relevant for gastrointestinal (GI) function and how allostatic load might cause disturbed gut function or gut symptoms.

It has been proposed that an integrative network of brain structures, involving hypothalamic subnuclei, the periaqueductal grey, and the amygdala mediate the stress response by providing output to pontomedullary areas and to the pituitary, which in turn modulate efferent autonomic and neuroendocrine control mechanisms of the organisms, causing alterations of GI motility.

EFFECTS OF STRESS ON GI MOTILITY IN HEALTHY CONTROLS: In humans, the available data clearly demonstrate that the most consistent pattern in the motility response of the GI tract to acute or short-term stress is an inhibition of gastric and intestinal motility but a stimulation of oesophageal and colonic motility. Gastrointestinal (colonic) motor responses to stress may vary depending on the nature of the stressor. One might propose, that these alterations play a pathophysiological role in dyspeptic symptoms and alterations in stool frequency and consistency in patients with stress related functional GI disorders. This idea is supported by indirect evidence from long-term studies in healthy volunteers, which showed that chronic stress causes symptoms consistent with the diagnosis of a functional gastrointestinal disorder.

EFFECTS OF STRESS ON GI MOTILITY IN FUNCTIONAL GASTROINTESTINAL DISORDERS: Distinct emotional responses to stress may induce differential (stomach) or more pronounced (colon) GI motor responses in functional gastrointestinal disorders, like the irritable bowel syndrome (IBS). The mechanisms underlying these differences in comparison to healthy subjects are so far not well understood. There is evidence that an increased emotional response is associated with this difference in colonic, and perhaps also gastric motor responses to certain stressors. In contrast, the available data do not support the idea that the stress-induced modulations of oesophageal or intestinal motility are different between IBS patients and controls. Thus, one might speculate that the genesis of stress related symptoms in functional gastrointestinal disorders, like IBS, are at least partially due to differential motility responses throughout the various regions of the GI tract.

It has been proposed, that persistent alterations of autonomic responsiveness play a role in altered gastric emptying and colonic transit in the most common functional gastrointestinal disorders, IBS and FD, but also in many of the extraintestinal complaints reported by such patients. However, almost no valid data are available so far from human studies, addressing the question whether differences in motility responses to stress between patients with functional gastrointestinal disorders and healthy subjects are due to either a) an altered stress response associated with an imbalance of the autonomic nervous system or b) increased stress susceptibility.

MECHANISMS OF STRESS EFFECTS ON GI MOTILITY IN EXPERIMENTAL ANIMALS: In experimental animals various stressors induce inhibition of gastric (and intestinal) motility but a stimulation of colonic motor function by autonomic mechanism, which is similar to the above-mentioned observations in humans. Endogenous CRF in the brain plays a significant role in the CNS mediation of stress-induced inhibition of upper GI and stimulation of lower GI motor function through activation of brain CRF receptors.

Specific autonomic brain nuclei are involved in the central CRF mediated motility responses of GI organs to stress. There is evidence that the paraventricular nucleus of the hypothalamus is involved in the CNS mediation of altered gastric and colonic motility due to stress and release of CRF in the brain. Locus coeruleus and dorsal vagal complex, respectively, seem to play a role in central CRF induced changes of colonic and gastric motility, respectively. The inhibition of gastric emptying by CRF may be mediated by interaction with the CRF-2 receptor, while CRF-1 receptors are involved in the colonic and anxiogenic responses to stress.
The available data from animal studies suggest that a hypersecretion of cerebral CRF could be involved in the pathophysiology of stress-related exacerbation of symptoms in IBS and other functional gastrointestinal disorders. Thus, in the future, CRF-1 antagonists might be of therapeutic value in IBS, particularly in patients with anxiety, depression and chronic stress.

Endogenous serotonin released peripherally in response to stress seems to be involved in stress- and central CRF-induced stimulation of colonic motility by acting on 5HT-3 receptors. Thus, 5HT-3 receptor antagonists are of considerable interest for the treatment of stress-induced GI symptoms, among other pathophysiological mechanisms resulting from stimulation of propulsive colonic motor function.

References (reviews):
EMOTIONAL AND COGNITIVE MODULATION OF GUT FEELINGS

Quazim Aziz
University Hospital of South Manchester, UK

BACKGROUND: Abdominal pain without an underlying organic cause is a characteristic of a number of common conditions collectively known as functional gastrointestinal disorders (FGID) and accounts for approximately 40 percent of all referrals to Gastroenterologists (1). Common characteristics of FGID are the presence of psychological co-morbidity and hypersensitivity to gut stimulation (2,3). Amongst the hypotheses proposed to explain these phenomena, one that has received much attention relates to aberrant brain processing of gut sensation, i.e. a non-painful stimulus is perceived as painful due to biased cognitive or impaired emotional response to the stimulus (4). Functional brain imaging techniques have been used to study brain gut interactions (5) and suggest that the brain processing of gut sensation is multidimensional and includes areas involved in sensory discrimination (primary and secondary sensory cortex), emotions and cognition (anterior insula, anterior cingulate and prefrontal cortices). Recent studies also suggest that emotional and cognitive factors modulate the brain processing of gastrointestinal sensation.

MODULATION BY EMOTIONS: The effects that emotional context has on the brain processing of oesophageal sensation in healthy subjects has recently been examined using functional Magnetic Resonance Imaging (fMRI). These studies demonstrate marked activation in bilateral insular and anterior cingulate cortices only when oesophageal stimulation is delivered during a negative emotional context, and not when it is presented during a neutral emotional context (6). This suggests that the brain processing of oesophageal sensation is modulated by the emotional context in which it is perceived. This observation provides a potential mechanism for the influence of negative mood states on symptom severity in FGID.

MODULATION BY COGNITIVE FACTORS: Normal gut function does not usually evoke sensory experience, therefore even innocuous sensations arising from the gut are novel and are often important signals of pending danger or potential harm and therefore can be of greater biological significance in comparison to other innocuous sensory input. The neural correlates of selectively focusing attention on either innocuous visual or gut stimuli have recently been studied in healthy volunteers, using fMRI (7). The results show that selectively focusing attention on gut stimuli, activates the sensory and cognitive neural networks to a greater extent in comparison to focusing attention on visual stimuli. This study provides empirical evidence that greater human brain neuronal resources are allocated to the biologically more novel or potentially more threatening sensory input. Exaggeration of this phenomenon may form the basis for hypervigilance to visceral sensation observed in patients with FGID.

CONCLUSION: Emotional and cognitive factors play an important role in modulating the brain processing of gut sensation. Studies of the brain gut axis may be useful in identifying FGID patients who have abnormal brain processing of gut sensation and these patients could then be treated with appropriate psychological therapies.

References:
Functional Gut Disorders

50-80% have evidence of Psychological Disorders

- Anxiety
- Depression
- Somatisation
- Panic Disorders

Visceral Hypersensitivity

Hypothesis - Abnormal Brain Processing

Emotions:
- Depression
- Anxiety

Cognition:
- Hypervigilance
Abdominal distension is an extremely common manifestation of IBS which appears to occur more frequently in females than males. The pathophysiology of this symptom is uncertain and it is not even clear whether it solely originates from the gut or whether an abnormality, such as anterior abdominal wall dysfunction, may also be contributory. Whatever the cause, patients certainly find distension a very intrusive problem and none of the current management strategies are particularly helpful. There is therefore a need to explore all the possible pathophysiological mechanisms further in order to establish the true nature of the problem and whether it has one or many causes.

References:
Intestinal gas, a frustrating problem for patients and their clinicians, has all too long remained a Cinderella topic in gastrointestinal physiology. A recent resurgence in interest in this field, coupled with a renewed appreciation of earlier classical studies, has permitted some progress; gas is beginning to reveal some of its malodorous secrets! Symptoms believed to be related to "gas" need to be carefully interpreted. An increase in gas production, which seems to be unlikely in IBS, leads to increased flatus production and evacuation but does not lead to distension and bloating. The pathogenesis of these symptoms is more obscure. Distension, often the most distressing "gas"-related symptom in IBS, has, until recently, been assumed to represent a disturbance of perception as apparently objective tests of abdominal volume failed to detect any increase in IBS. This assumption has now been questioned; distension may reflect the combined effects of gas retention, leading to true distension, and visceral hypersensitivity. Detailed, dynamic studies of changes in distension over time, coupled with observations of gas transit may finally reveal the origins of these symptoms, in IBS. Visceral hypersensitivity, apparently ubiquitous in IBS, could render the individual highly sensitive to subtle changes in gas production, transit or evacuation.
Gas in IBS

- Flatus = Production – probably normal.
- Bloating = retention
  visceral perception/sensation

Flatus excretion

Bloating score
FOOD INTOLERANCE AND THE IRRITABLE BOWEL SYNDROME

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Many patients with irritable bowel syndrome (IBS) improve considerably when they follow a diet avoiding specific foodstuffs, particularly cereals, dairy products, yeast and caffeine. In our original study, food reactions were confirmed on double-blind challenge using nasogastric tubes, and positive challenges were associated with a dramatic increase in the production of rectal prostaglandins. In later studies 122 out of 182 successive patients succeeded in gaining dietary control of their symptoms. From this experience it has been possible to develop exclusion diets which provide a straightforward way of detecting patients’ food intolerances. Other workers have confirmed our findings.

Despite the link with food, no evidence of classical food allergy exists, and research has concentrated on elucidating the mechanisms of food intolerance.

IBS has been shown in prospective studies to arise following gastroenteritis and antibiotic therapy, and the bacterial flora of the colon in IBS is unstable, with overgrowth of facultative anaerobes and a reduction in the number of lactic acid bacteria. Because of this, we studied colonic fermentation in IBS patients and normal controls. Subjects spent 24 hours in a purpose-built calorimeter through which air was drawn at a constant rate, allowing repeated sampling of gases released on the breath and in rectal flatus. The maximum rate of gas excretion was significantly greater in patients than controls and hydrogen production was higher. In patients an exclusion diet produced a considerable fall in maximal gas excretion. Further studies have shown that gas production is also less after antibiotics and enteral feeds, and that symptoms improve in parallel with reductions in gas production. Production of fermentation gases in patients unresponsive to exclusion diets was not different from controls.

IBS is not a homogenous condition, and other mechanisms may also be responsible for the production of gastrointestinal symptoms. These include anxiety and air-swallowing, menstrual disturbances, and constipation. A history of IBS arising after gastroenteritis or repeated courses of antibiotics is a strong indication for the trial of an exclusion diet, however, in as many as 50% of IBS patients symptoms are caused by abnormal fermentation of specific food residues as a result of damage to the colonic microflora.

References:
Notes
Probiotics are living microorganisms (such as lactobacilli strains, bifidobacteria, certain non pathogenic Escherichia coli strains, and the non-toxic yeast Saccharomyces boulardii) that on ingestion exert health beneficial benefits beyond inherent general nutrition (1). One of the most important criteria which must be fulfilled for a clinical applicable probiotic is that it must be capable of colonizing the intestinal tract and that it can attach to human intestinal mucosal cells (2). The cross talk between the probiotic and the host may lead to displacement of intestinal pathogens and it can activate membrane receptors that can influence our immune system, including development of oral tolerance, that is essential for optimal processing of nutrients, it may affect motor functions, and it can reduce mucosal permeability defects. Probiotics also alter the composition the flora by production of lactic acid, bacteriocins and antimicrobial peptides, which are active against pathogens. Additional benefits include production of mucosal micronutrients, elimination of toxins and reduction in fecal ammonia, which is toxic to the mucosa.

A rationale for treatment of gastrointestinal diseases is emerging: probiotic lactobacilli are effective in the treatment of Clostridium difficile and rotavirus diarrheas (3), preliminary results in animal models and humans with IBD are encouraging (4), successful maintenance treatment of chronic pouchitis (5).

There is also a rationale for treatment of IBS with probiotics because in IBS it is common knowledge that symptoms are related to food intake, endocrine imbalance, and disturbance of the intestinal flora. The prevalence of an abnormal 14C-xylose breath test demonstrating small bowel bacterial overgrowth was 56% and 29% in diarrhea and constipation predominant IBS, respectively (6). It was also demonstrated that IBS patients treated with metronidazole were better than placebo-treated patients, suggesting that bacteria may play a role in the symptoms of IBS (7) An other more recent study also showed that eradication of small intestinal bacterial overgrowth eliminates IBS symptoms in 48% of the subjects. It is interesting to mention that of the 202 selected IBS patients in this study 157 (78%) had small bowel bacterial overgrowth (8). The only study published in which IBS patients were treated with the probiotic Lactobacillus plantarum showed that abdominal pain and flatulence was significantly reduced (9).

It is clear from these preliminary studies that the value of probiotics as preventive therapy for a variety of gastrointestinal disorders including IBS looks promising but we need to perform more double-blind placebo controlled investigations. By developing future studies we should realize that one of the major problems is that we don’t know which organism is useful for which condition. Furthermore, fulfillment of the therapeutic potential of probiotics is likely to require more complete understanding of normal intestinal flora (4).

References:

5HT AND IBS

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Approximately 80% of the human body 5-hydroxytryptamine (5-HT) is located in the gastrointestinal tract, with 95% residing in the enteroendocrine cells and 5% in the neurons of the myenteric plexus that use 5-HT as a transmitter. The remaining 5-HT is found either in the brain or the platelets. Virtually all of the 5-HT in the plasma is derived from the gastrointestinal tract (1,2) where platelets rapidly take it up and store it in dense granules (3). 5-HT is also removed from the circulation by being degraded in the liver and kidney by monoamine oxidase and aldehyde dehydrogenase to 5-hydroxyindole acetic acid (5-HIAA), which is then excreted in the urine (4). 5-HT is released from enteroendocrine cells by a number of stimuli including the chemical constituents of food, distension of the gut, stress and even toxins and cell damage (5). The released 5-HT then acts via a number of 5-HT receptors (particularly the 5-HT3 and 5-HT4 receptors) to control the sensory, motility and secretory functions of the gastrointestinal tract. Disordered function can lead to for example nausea, vomiting, abdominal pain and diarrhoea.

Irritable bowel syndrome (IBS) in often associated with altered motility and sensory function, suggesting a possible link with 5-HT. This is supported by recent preliminary findings that platelet poor plasma 5-HT concentration is elevated following meal ingestion in patients with diarrhoea predominant IBS compared with healthy controls (6) and that those patients who experience post-prandial symptoms have higher levels of platelet depleted plasma 5-HT than those who do not (7). Furthermore, patients with IBS appear to have larger platelet stores of 5-HT than healthy volunteers (8), supporting increased exposure of their platelets to circulating levels of plasma 5-HT. Other studies have suggested abnormal enteroendocrine cell numbers (9) and mucosal 5-HT concentrations (10) in patients with IBS.

Drugs targeting these receptors may therefore be a rational approach to the treatment of IBS. To date these have included the development of a number of 5-HT3 receptor antagonists (eg granisetron, ondansetron, alosetron, cilansetron) and 5-HT4 receptor agonists (cisapride, prucalopride, tegaserod) for the treatment of diarrhoea and constipation predominant IBS, respectively (11). Three of these may progress to become licensed medications (cilansetron, prucalopride, tegaserod).

References:

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