THIRD ANNUAL MEETING OF THE NEUROGASTROENTEROLOGY AND MOTILITY SECTION OF THE BSG

PROGRAMME AND ABSTRACTS

26TH SEPTEMBER 2003

ROYAL COLLEGE OF PHYSICIANS, LONDON
THIRD ANNUAL MEETING OF THE NEUROGASTROENTEROLOGY AND MOTILITY SECTION OF THE BSG

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Dear Colleague

On behalf of the Neurogastroenterology and Motility Section of the BSG, we are pleased to be able to welcome you to the RCP. The section, which was founded just two years ago, now has 101 members. In addition to two highly successful symposia at the 2002 & 2003 BSG meetings, we have also held two stand-alone meetings at Robinson College Cambridge in September 2001 and at the Royal College in September 2002. The current meeting is the third of these more specialised stand alone meetings, designed to increase interest in, and understanding of, disorders of Neurogastroenterology

This 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 with outstanding speakers. The areas covered reflect some exciting new developments of both understanding and treatment in Neurogastroenterology. We have tried to combine both theory and practice within the varied programme. We hope that you will enjoy the meeting and add to its value by actively participating with comments and questions. I am pleased to confirm that the Royal College of Physicians has once again accredited the meeting for four hours of CME.

Best wishes

Professor Robin Spiller
Chairman
Neurogastroenterology and Motility Section
British Society of Gastroenterology
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<td>Dietary influences on GI endocrine secretions and their relevance to satiety</td>
<td>Graham Dockray</td>
<td>University of Liverpool</td>
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<tr>
<td>10.30 - 11.00</td>
<td>Ghrelin and its role in appetite control</td>
<td>Alison Wren</td>
<td>Royal Postgraduate Medical School, London</td>
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<td>11.00 - 11.30</td>
<td>Coffee Break</td>
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<td>11.30 - 12.00</td>
<td>The representation of the taste and other sensory properties of food in the brain in relation to appetite control and obesity</td>
<td>Edmund Rolls</td>
<td>University of Oxford</td>
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<td>12.00 - 12.30</td>
<td>Energy regulation in obesity: Where is the defect?</td>
<td>Paul Trayhurn</td>
<td>University of Liverpool</td>
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<td>12.30 - 13.30</td>
<td>Lunch</td>
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**Afternoon Session Chaired by Qazim Aziz & Praveen Anand**

**Understanding the Neuropathology of the Gut**

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<td>13.30 - 14.00</td>
<td>Mechanisms of pain in peripheral neuropathy and their relevance to GI disorders</td>
<td>Praveen Anand</td>
<td>Royal Postgraduate Medical School, Hammersmith Hospital, London</td>
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<td>14.00 - 14.30</td>
<td>Neurological disease of the bladder in relation to bowel dysfunction</td>
<td>Clare Fowler</td>
<td>National Hospital for Nervous Diseases, London</td>
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<td>14.30 - 15.00</td>
<td>Neuropathology of pseudo-obstruction and IBS</td>
<td>Greger Lindberg</td>
<td>Karolinska Institute, Stockholm</td>
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<td>15.00 - 15.30</td>
<td>Bowel dysfunction in neurological diseases</td>
<td>Anton Emmanuel</td>
<td>St Mark’s Hospital, London</td>
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FACULTY

Professor Praveen Anand
Professor of Clinical Neurology
Peripheral Neuropathy Unit, Hammersmith Hospital, London, UK

Professor Praveen Anand is Professor of Clinical Neurology and Head of the Peripheral Neuropathy Unit at Imperial College London, based at Hammersmith Hospital. His medical education was at the Universities of Oxford and Cambridge, and postgraduate training was at the Hammersmith Hospital and the National Hospital for Neurology and Neurosurgery, Queen Square, London. His research focuses on pathophysiological and molecular mechanisms in the human sensory neuropathies, funded by the MRC, Wellcome Trust, other research charities and biotechnology/pharmaceutical companies. Collaborations with pharmaceutical companies are directed to projects which bridge the gap between pre-clinical developments and successful clinical applications.

Professor Graham Dockray
Professor of Physiology
Department of Physiology, University of Liverpool, Liverpool, UK

Graham Dockray trained in the University of Nottingham, and was a Fogarty International Fellow of the NIH in the laboratory of Dr Morton Grossman (Los Angeles). He is presently Head of the Department of Physiology at the University of Liverpool. His research interests are in the biology of gut endocrine cells, the control of epithelial organization and signalling from gut to brain. His research work has been continuously supported by the MRC since 1976, including programme grant support since 1988. He is a fellow of the Academy of Medical Sciences and an honorary Fellow of the Royal College of Physicians. He has authored or coauthored over 230 papers in peer review journals including Nature, J.Clin.Invest., Gastroenterology, J.Biol.Chem., J.Physiol. and Am.J.Physiol.
Dr Anton Emmanuel  
*Senior Lecturer and Consultant Gastroenterologist*  
*St Mark’s Hospital, London, UK*

Anton Emmanuel graduated from London University in 1990 and became a member of the Royal College of Physicians (London) in 1993. He trained in gastroenterology in London and undertook research into aspects of extrinsic autonomic control of gut function, at St Mark’s Hospital, under the supervision of Professor Michael Kamm. This work formed the basis of a doctorate degree (MD) from London University awarded in 2000. He developed and validated a novel technique for measuring extrinsic autonomic innervation to the gut. His current research includes in vitro study of gut afferents, research into the control of gut reflexes (which has particular bearing in terms of understanding gut dysfunction after spinal cord injury) and pharmacological and psychological therapies in chronic abdominal pain. He is also very involved with research into the role of ghrelin and other orexigenic peptides, both in vitro and in patients. Related to this work are studies into the pathophysiological changes that occur in the gut in type one diabetes.

Anton Emmanuel was appointed to the permanent position of Senior Lecturer with Imperial College and Consultant Gastroenterologist at St Mark’s in 2000. His clinical practice encompasses the full spectrum of lumenal gastroenterology and endoscopy. In 2002 he was appointed honorary consultant gastroenterologist to the Spinal Injuries Unit at the Royal National Orthopaedic Hospital.

Anton Emmanuel is on the advisory board of the Royal College of Physicians with regard to Bowel Care. He is heavily involved in co-ordinating undergraduate teaching with Imperial College. He is College Tutor for St Mark’s Hospital, and represents the Hospital on the Gastroenterology Specialist Training Committee. He currently supervises two undergraduate and three postgraduate research fellows.

Professor Clare J Fowler  
*Professor of Uro-Neurology*  
*Institute of Neurology, University College London and Consultant at the National Hospital for Neurology & Neurosurgery, UCLH*  
*London, UK*

Professor Fowler qualified in medicine from the Middlesex Hospital in London, and went on to study neurology. She furthered her burgeoning interest in physiology with an MRC funded MSc, following which she took a post as research registrar at the Institute of Neurology. When she returned to clinical medicine it was to specialise in clinical neurophysiology. She was appointed a consultant in 1987, holding posts at both St Barthlomew’s and the Middlesex Hospitals. Her interests then focussed on the neurophysiology and neurology of pelvic organs and she is currently Professor of Uro-Neurology at the Institute of Urology and Institute of Neurology and Consultant at the National Hospital for Neurology and Neurosurgery.

An acknowledged international expert on neurogenic urinary incontinence and erectile dysfunction, Professor Fowler is widely published and has extensive clinical trials experience in these areas. As well as her membership of many international and national professional societies, Professor Fowler finds time for an active involvement in the management of UCLH.
Professor Greger V V Lindberg  
*Associate Professor of Medicine*  
*Karolinska Institute, Stockholm, Sweden*

Professor Lindberg graduated from the Medical School at Karolinska Institutet in 1978 and following qualifications as a Specialist in Internal Medicine and in Gastroenterology, he was appointed Consultant Gastroenterologist in 1991. In 1996, surgeons and physicians at Huddinge University Hospital joined to form the Centre for Gastroenterology where he works today as both Head of the GI Physiology Laboratory and Head of the Out-Patient Clinic. He was appointed to his current position of Associate Professor of Medicine at Karolinska Institutet in 1991.

Professor Lindberg has been involved with clinical research since 1975 and his early research concerned medical decision making and computer assisted diagnosis. Following a PhD on "Studies on Diagnostic Decision Making in Jaundice", he went on to study the pathogenesis, differential diagnosis, and treatment of patients with various forms of dyspepsia. This led to a growing interest in gastrointestinal motility. He learnt about intestinal manometry at the Royal London Hospital, Whitechapel and was involved in the development of a technique for ambulatory monitoring of small bowel motility, which became an important tool for the study of patients with suspected motility disorders. They took the diagnosis one step further by exploring the underlying structural abnormalities in laparoscopy-assisted full thickness biopsies of the jejunum, using intestinal pseudo-obstruction as a model disease. This led to his current main area of research interest, pathogenetic and aetiological factors in functional bowel disorders. Professor Lindberg’s research in this area has resulted in many publications, including 60 original papers, 22 books and book chapters, and 11 overviews.

Professor Edmund T. Rolls  
*Professor of Experimental Psychology at The University of Oxford.*  
*Fellow and Tutor in Psychology at Corpus Christi College, Oxford, UK*

Educated at the University of Cambridge, Professor Edmund T Rolls was awarded an M.A. in Natural Science and went on to train in neuroscience research at the University of Oxford, where he was awarded the Degrees of Doctor of Philosophy (in Psychology) and Doctor of Science. As well as his role as Professor of Experimental Psychology, Professor Rolls is Associate Director of the Medical Research Council Interdisciplinary Research Centre for Cognitive Neuroscience at the University of Oxford.

Professor Rolls is a neuroscientist with research interests in the neurophysiology of vision; the neurophysiology of taste, olfaction and feeding; neural mechanisms of memory and emotion; the neurophysiology of the basal ganglia; the operation of real neuronal networks in the brain; and brain processes underlying consciousness. He has published more than 320 full length research papers on these topics and has also written, edited or contributed to a number of key neuroscience textbooks. His expertise has led to key roles in the European Neuroscience Association and European Brain and Behaviour Society and he has also been awarded honorary membership of La Socite Francaise de Neurologie and the Danish Neuropsychological Society. More recent distinctions include the Kenneth Craik Research Award from St John’s College, Cambridge in 2000/2001. His web site is [www.cns.ox.ac.uk](http://www.cns.ox.ac.uk)
**Professor Paul Trayhurn**  
*Professor of Obesity Biology and Unit Director*  
*University of Liverpool, UK*

Professor Trayhurn holds a BSc in Physiology & Biochemistry from the University of Reading, a DPhil and DSc from the University of Oxford (1972) and was elected to Fellowship of the Royal Society of Edinburgh (FRSE) in 1997. His previous appointments include: NATO European Research Fellowship, Strasbourg; Scientific Staff, MRC Dunn Nutrition Laboratory, Cambridge; Professor and Heritage Scholar in Nutrition & Metabolism, University of Alberta; Head, Division of Biomedical Science, Rowett Research Institute, Aberdeen; Honorary Professor, University of Aberdeen; and Professor of Nutritional Biology, University of Oslo, Norway. He was appointed to the Chair of Obesity Biology at Liverpool in 2001.

He has worked on the regulation of energy balance and the aetiology of obesity since 1975 and his early studies were concerned with the efficiency of energy utilisation and the mechanisms of adaptive changes in energy expenditure. This led to an interest in thermogenesis and its molecular basis in brown adipose tissue through uncoupling protein-1. Since 1994 the focus of his programme has moved to white adipose tissue, initially through studies on the biology of the cytokine-like hormone, leptin. His current interests are centred on the secretory and endocrine role of adipose tissue - the nature, regulation and function of the various secretory factors produced by the tissue (e.g. leptin, resistin, adiponectin, cytokines and metallothionein).

Professor Trayhurn is currently Editor-in-Chief of the British Journal of Nutrition, a member of the Editorial Board of the International Journal of Food Sciences and Nutrition and on the Advisory Board of the new Electronic Journal of Environmental, Agricultural and Food Chemistry. Among his other current activities, he is Chair of the Awards Committee of the International Association for the Study of Obesity and a Member of the Advisory Board of the UK Medical Research Council.

**Dr Alison Wren**  
*Clinical Research Training Fellow*  
*Imperial College at Hammersmith Campus, London, UK*

Dr Wren qualified from the University of Newcastle-Upon-Tyne in 1993 and, after junior posts in general medicine at Queens Medical Centre, Nottingham, moved to London to undertake further training in Endocrinology. In 1999, after completing 2 years of clinical training at Southend, Hillingdon, Barnet and Hammersmith Hospitals, she obtained her current post as a Wellcome Clinical Research Training Fellow under the supervision of Professor Steve Bloom at Imperial College, Hammersmith Campus. Professor Bloom’s group are renowned for their work on elucidating the physiological actions of gut hormones and the mechanisms of hypothalamic regulation of energy balance, having published over 1500 papers in this field. Dr Wren’s research has particularly focused on the role in energy balance of ghrelin, a recently discovered gastric hormone and endogenous ligand for the growth hormone secretagogue receptor. She lives with her family in London and enjoys yoga, sailing and playing with her one year old son.
THIRD ANNUAL MEETING OF THE NEUROGASTROENTEROLOGY AND MOTILITY SECTION OF THE BSG

ABSTRACTS
Peripheral signals, many of gut origin, regulate food intake. These mechanisms have often been considered to provide short-term inhibition of food intake, but recent work suggests the system is more complex.

Multiple peptides released from enteroendocrine cells are implicated in the control of appetite. Hormones released from both proximal and distal intestinal enteroendocrine cells are associated with inhibition of food-intake e.g. CCK, GLP-1, PYY; in addition, peptides released from gastric endocrine cells may stimulate food intake e.g. ghrelin, orexin A. The routes by which these peptides influence the CNS include actions on vagal afferent nerve fibres and delivery by the circulation to the brain stem or the hypothalamus.

Enteroendocrine cells are specialised for luminal nutrient sensing, although sub-epithelial nerve fibres may also respond to luminal chemicals that freely diffuse across the epithelium e.g. short chain fatty acids, and to non-nutrient signals e.g. gastric distension. The molecular recognition mechanisms involved in nutrient sensing can be highly specific; for example, fatty acids with a chain length greater than C12 release CCK but those with shorter chain lengths do not. There has been considerable interest recently in sensing mechanisms involving G-protein coupled receptors GPCRs; examples include GPCRs responding to fatty acids, to extracellular Ca\(^{2+}\) and aromatic amino acids, to sweet and to bitter compounds.

There is integration of dietary signals at the level of enteroendocrine cells, where for example both apical i.e. luminal, and basolateral stimuli e.g. growth factors, cytokines and neurohumoral agents, regulate the secretion of regulatory peptides. There is also integration of stimuli at the level of afferent neurones; for example, CCK acts on primary afferent nerve fibres of the vagal trunk that also express leptin receptors [thought to respond to leptin released from gastric chief cells] and orexin receptors activation of which inhibits the effects of CCK. These various signalling mechanisms allow specific responses to be matched to meals of different contents.

References
Obesity is the major cause of morbidity and mortality in the UK and is associated with over 1000 premature deaths per week in the UK alone. Further, the prevalence of obesity is increasing worldwide and now includes a significant number of children. Advice to the population to reduce food intake and increase exercise has been unsuccessful in altering this trend. As yet, except for bariatric surgery, there is no adequately effective treatment for this pandemic of obesity.

Recent work has focused on the role of gastrointestinal hormones acting as nutrient sensors in the gut and signalling to the brain to trigger meal initiation and termination as well as regulating longer term energy balance. One of these hormones, ghrelin, a recently identified endogenous ligand for the growth hormone secretagogue receptor, is synthesized predominantly in the stomach. Ghrelin has been shown to stimulate appetite and food intake in rodents and man and promote weight gain and adiposity in rodents. In man, circulating levels of ghrelin exhibit diurnal variation, peaking before each meal and falling to trough levels within an hour of eating, suggesting a role for ghrelin in meal initiation. Ghrelin is also increased by longer term negative energy balance and reduced by positive energy balance. These changes are the converse of those found for the adipocyte hormone leptin. Thus it appears that ghrelin is part of a dynamic feedback system in the regulation of body weight. Ghrelin has a novel acyl side-chain modification, which is essential for biological action. It was hypothesized that this may facilitate passage across the blood brain barrier, however, in a recent report, acylated ghrelin readily crossed the blood-brain barrier in the brain to blood direction, but there was negligible transport in the blood to brain direction. There is evidence to suggest that circulating ghrelin may, rather, act via vagal afferents. However, it has been demonstrated that ghrelin can also act directly on hypothalamic nuclei, particularly the arcuate nucleus, to stimulate food intake. It is possible that this reflects a role of endogenous neuronally-derived hypothalamic ghrelin, rather than circulating ghrelin.

Thus ghrelin joins an increasing number of gastrointestinal/CNS peptides that appear to have important homeostatic functions, including the regulation of energy balance. Alteration of ghrelin and other gastrointestinal hormones following gastrointestinal bypass operations may contribute to the astonishing success of these procedures in producing dramatic and sustained weight loss. Ghrelin and other gut hormones are released every day without side effects and continue to exert their effect without escape. There is, thus, a good chance that gut hormones will offer a long-term therapeutic approach to weight control without deleterious side effects. This hypothesis needs testing.

References
THE REPRESENTATION OF THE TASTE AND OTHER SENSORY PROPERTIES OF FOOD IN THE BRAIN IN RELATION TO APPETITE CONTROL AND OBESITY.

Professor Edmund T. Rolls
University of Oxford, Department of Experimental Psychology, Oxford, UK

During a meal, the pleasantness of the taste, smell, sight and texture of the food being eaten decreases to zero, while other can foods remain pleasant. This is sensory-specific satiety. As a result, much more food is eaten if variety is provided, and sensory-specific satiety is a major determinant of the amount of food eaten in a meal1. Sensory-specific satiety is not represented in the primate primary taste cortex or inferior temporal visual cortex, where neurons are not affected by feeding to satiety. These areas represent the identity of the stimulus. In the primate orbitofrontal cortex, neurons show sensory-specific satiety-related effects, decreasing their responses to the sight, taste, odour and texture (e.g. fat texture) of food to zero during feeding to satiety. Some sensory-specific satiety can be produced simply by tasting, smelling etc the food for 10 minutes without swallowing. These findings provide evidence that sensory-specific satiety is implemented by habituation with a time course of approximately 10 min of synaptic afferents onto orbitofrontal cortex neurons which represent the reward value or pleasantness of food, combined with a feedback effect of gastric distension. The neurophysiological studies show that ensemble encoding is used in the orbitofrontal cortex to provide a rich representation of the properties of foods, including its taste, smell, texture, and sight. Recent neuroimaging studies show that sensory-specific satiety is reflected in activations found in the human orbitofrontal cortex.

References
10. Kringelbach ML, O’Doherty J, Rolls ET and Andrews C. Activation of the human orbitofrontal cortex to a liquid food stimulus is correlated with its subjective pleasantness. Cerebral Cortex 2003;13, in press.

Publications available at www.cns.ox.ac.uk
ENERGY REGULATION IN OBESITY – WHERE IS THE DEFECT?

Professor Paul Trayhurn  
Neuroendocrine & Obesity Biology Unit, Department of Medicine, University of Liverpool, Liverpool L69 3GA, U.K.

The incidence of obesity is rising rapidly in the U.K., with some 20% of adults now being obese (BMI>30) and over half the population overweight (BMI>25). The rapid rise in obesity is a consequence of changes in lifestyle, but it has provided impetus to the investigation of the fundamental mechanisms involved in the control of energy balance. In the genomic era, this has included a search for those genes, or gene polymorphisms, which predispose to obesity. At a mechanistic level, important developments have occurred recently in the identification of novel neuropeptides involved in the control of appetite, such as CART (cocaine- and amphetamine-regulated transcript) and the orexins, while the discovery of new uncoupling proteins (UCP2, UCP3) was initially thought to provide a locus for adaptive thermogenesis in skeletal muscle and other organs outwith brown fat. A radical change in perspective on energy balance has come from new understanding of the functions of white adipose tissue (WAT). The traditional view that WAT is simply a fat storage depot has been replaced by the recognition that it is an endocrine organ, communicating both with the brain (particularly the hypothalamus) and peripheral tissues through the release of the cytokine-like hormone, leptin. Leptin is secreted principally from adipocytes, but is also synthesised in the stomach and elsewhere, and acts as a critical signal in energy balance. Leptin is not, however, the only protein signal secreted by WAT. Indeed, there is a rapidly growing list of such factors, and this includes the hormones adiponectin and resistin (implicated in insulin resistance), classical cytokines such as IL-6 and TNFα, and proteins involved in vascular haemostasis (e.g. plasminogen activator inhibitor-1). Unravelling the fundamental biology of energy balance will aid the development of new therapeutic approaches to the treatment of obesity.
MECHANISMS OF PAIN IN PERIPHERAL NEUROPATHY AND THEIR RELEVANCE TO GI DISORDERS

Professor Praveen Anand
Imperial College at Hammersmith Campus, London, UK

The recent discovery of receptors which respond to capsaicin, low pH, temperature, menthol and ATP, and their expression in subsets of sensory nerve fibres, provides a prospect to advance understanding and treatment of somatic and visceral sensory dysfunction. We have studied their role in chronic human neuropathic pain and hypersensitivity states, including rectal hypersensitivity / irritable bowel syndrome, inflammatory bowel disease, urinary bladder overactivity and hypersensitivity, vulvodynia, and breast pain with tenderness. These studies reveal common mechanisms, such as the up-regulation of the capsaicin receptor VR1 (TRPV1) by nerve growth factor (NGF). TRPV1 has been shown to be present predominantly in small diameter primary sensory neurons, and is involved in nociception. TRPV1 was significantly increased in somatic nerves after injury. In rectal hypersensitivity, VR1-immunoreactive nerve fibres were increased in muscle, submucosal and mucosal layers. The VR1 increase correlated significantly with lowered rectal heat and distension sensory thresholds. Heat and distension thresholds were also significantly correlated. Faecal urgency and rectal hypersensitivity thus appears to involve increased numbers of nerve fibres expressing VR1. These are likely to be polymodal sensory fibres, regulated by NGF and GDNF. The triggering factor(s) remains uncertain, but drugs that target VR1-expressing nerve terminals, such as topical resiniferatoxin or novel VR1 blockers, deserve clinical trials. VR1, P2X3 and ASICs were up-regulated in IBD, but their differential expression in sensory/enteric neurons suggest distinct pathological effects. In urinary bladder, VR1- and P2X3-immunoreactive fibres were increased in overactive bladder states, and both were significantly reduced after intravesical RTX treatment only in patients with functional improvement, suggesting co-expression in polymodal afferents. Vulvodynia is characterised by painful burning sensation and allostynia in the region of the vulval vestibulus. We found increased papillary VR1 fibres in vulvodynia tissues. Breast pain and tenderness have been attributed to stretching of the nerves with increase in breast size, but tissue mechanisms are unknown. We have recently observed that capsaicin receptor VR1-positive intra-epidermal fibres were significantly increased in patients with breast pain and tenderness. A number of common pain states, including the “dynias” and visceral hypersensitivity, are thus marked by changes in these newly discovered receptors, particularly VR1, which represent disease markers and potential therapeutic targets.
Sensory Ion Channels and Receptors

- Capsaicin receptor VR1 (TRPV1)
- Acid sensing ion channels (ASICs)
- P2X3 (activated by ATP)
- IK1 (Ca+ activated potassium channel)
- SNS/PN3 (Nav1.8) (TTX-R sodium channel)
NEUROLOGICAL DISEASE OF THE BLADDER IN RELATION TO BOWEL DYSFUNCTION

Professor Clare J. Fowler
Institute of Neurology and Institute of Urology, UCL And National Hospital for Neurology and Neurosurgery, UCLH

The neurological control of the bladder is highly complex and for physiological control, extensive connections between the frontal lobes, brain stem and sacral spinal cord must be intact. Not surprisingly bladder dysfunction is common in patients with neurological disease. Disorders of bowel function are not, however, a regular accompanying complaint and may have a separate and different pathophysiological basis if they do occur.

The commonest site of a neurological lesion causing bladder dysfunction is the spinal cord. Following spinal cord damage the pontine micturition centres become disconnected from the sacral spinal cord, resulting in the emergence of a new functional pathway. The afferent limb of the reflex arc is formed by formerly silent unmyelinated bladder afferents that respond to bladder filling and cause reflex detrusor contraction. The resulting clinical picture is due to detrusor overactivity which clinically presents as urgency, frequency and urge incontinence. The same pathophysiology does not seem to regularly affect the bowel. Thus the bowel complaints that patients do complain of in spinal cord disease are related more to loss of sensation and a failure of voluntarily control of ano-rectal structures and probably a loss of the ability to exhibit the "pro-continence reaction" i.e. contraction of the pelvic floor and sphincters in response to sensing impending, inappropriate elimination.

When neurological disease affects the higher functions involved in the social monitoring of elimination both bladder and bowel control may be involved, but such cases are rare. Common neural controlling pathways for bladder and bowel exist in the sacral roots and distally so that both functions are affected in patients with cauda equina lesions and extensive small fibre peripheral neuropathies.

However an area of growing clinical interest is a group of patients who present with disorders of bladder emptying and severe constipation. It seems likely that the pathology in this group may lie in the intrinsic neuromuscular controlling mechanisms of both the gut and bladder. Theoretically, possible causes include disorders of the afferent or efferent innervation of the viscera that are involved in local controlling neural pathways, smooth muscle myopathies or possibly channelopathies affecting the various neuromuscular structures necessary for physiological function. Currently there is active research interest in the intrinsic neural circuitry of the bladder and similarities are being proposed between cells identified in the suburothelial layers of the bladder and gut Interstitial Cells of Cajal. It may be that common protein expression of these structures means that an autoimmune or degenerative process can affect mechanisms of both organs, resulting in the as yet poorly understood clinical disorders.

References
**Neurological Disease and the Bladder**

- Neurological control of bladder is highly complex requiring extensive pathways of the nervous system to be intact for physiological control
- Frequency affected in neurological disease
- Commonest neurological cause of bladder dysfunction is a disconnection of the controlling centres in the pons from the sacral segments of the spinal cord

**Consequences of spinal cord disease for bladder dysfunction**

- In spinal health afferent information about bladder filling is relayed to the PAG by small myelinated fibres and thence to pontine micturition centres
- Following disconnection a sacral spinal segmental reflex emerges the afferent limb of which are formerly “silent C fibres”
- The bladder then develops reflex contractions on filling (i.e. detrusor overactivity) which may cause urgency and urge incontinence
- The same pathophysiology does not appear to affect the lower bowel

**Neurogenic Disorders which affect bladder and bowel function**

- Disorders of higher centres involved in social planning of continence
- Spinal cord disease
- Cauda equina lesions
- Peripheral neuropathy affecting small fibres
- Disorders of intrinsic innervation of bladder and gut
  - Autonomic neuropathies
  - Smooth muscle myopathies
  - ?channelopathies affecting neuro-muscular control of both functions
Intestinal pseudo-obstruction is a rare group of diseases that are characterised by severely disturbed motor function of the gastrointestinal tract. Two main types of pseudo-obstruction are recognised at histopathology: myopathic pseudo-obstruction when smooth muscle cells are affected and neuropathic pseudo-obstruction caused by damage to extrinsic or intrinsic nerves. Damage to the neurones of the myenteric plexus seems to lead to contractile hyperactivity whereas at least advanced myopathy is accompanied by severe hypomotility.

The myenteric plexus, which is involved in most motor events of the gut, is situated deep in the bowel wall between the inner circular and the outer longitudinal muscle layers. This part of the enteric nervous system is therefore inaccessible through mucosal biopsies taken for example at endoscopy. In order to study the pathology of the myenteric plexus or the muscle layers it is necessary to obtain full thickness biopsies of the entire bowel wall. Previously full thickness biopsies were obtained at bowel resection or from laparotomy in highly selected cases. With the advent of the laparoscopy-assisted technique for full thickness biopsy of the small bowel the neuropathologic examination of the myenteric plexus has become considerably easier to attain. Briefly, the method that we have used is to identify by laparoscopy a suitable loop of the jejunum, which is then exteriorised for biopsy taking. Part of the biopsy is used for ordinary transversal cuts but part of the biopsy is fixated for tangential cuts, which allows for staining and visualisation of large areas of the myenteric plexus. Modern immunohistochemical stains have made it easier and more reliable to study pathologic features of the myenteric plexus compared to silver staining. Immunohistochemistry has also facilitated the study of myopathic features.

In a prospective series of 72 patients with intestinal pseudo-obstruction we found that 48 (67%) had visceral neuropathy, 19 (26%) had visceral myopathy and 5 (7%) had a combined neuro-myopathy. The most common type of neuropathic lesion was inflammatory neuropathy which was found in 31 (43%) of patients. Dense infiltration of T-lymphocytes into the myenteric plexus was seen in 7 patients but in 23 patients the inflammation consisted of a low-grade infiltration of 2-10 T-lymphocytes per ganglion. One patient had an isolated inflammation along the axons. One third of the patients with inflammatory neuropathy also showed an increased number of lymphocytes in the mucosa. A large proportion of those with inflammatory neuropathy also had hypertrophy of the outer longitudinal muscle layer. This was believed to be secondary to the neuropathic changes and not a true myopathy.

The combination of epithelial and ganglionic inflammation was found also in full thickness biopsies from patients with other motility disturbances such as slow transit constipation, severe functional dyspepsia and the irritable bowel syndrome. This points at a discrepancy between histopathological findings and type and severity of the corresponding motility disorder. In a small series of full thickness biopsies of the jejunum from patients with severe irritable bowel syndrome we found low-grade inflammation of the myenteric plexus in 9/10 patients and a degenerative neuropathy in the tenth patient.

Although histopathologic findings may not seem to correlate well with the clinical picture, we must remember that our current diagnostic labels only pertain to collections of symptoms and these do not tell us anything about causation. Histopathology may direct us at least to some of the causes for gastrointestinal motility disorders.

References

**Biopsy preparation**

![Biopsy preparation diagram](image)

**Morphological findings in adult CIP**

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<td>Inflammatory neuropathy</td>
<td>43%</td>
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<tr>
<td>Degenerative neuropathy</td>
<td>19%</td>
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<td>Other neuropathies</td>
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<table>
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<th>Visceral myopathy</th>
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<tr>
<td>Degenerative myopathy</td>
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<tr>
<td>Abnormal architecture</td>
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<td>Other myopathies</td>
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**Combined neuro-myopathy** | 7%

**Pathology in IBS**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>IBS type</th>
<th>Disease duration</th>
<th>Myenteric lymphocytes</th>
<th>IEL/100 ep.c.</th>
<th>Neuronal degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (F)</td>
<td>C</td>
<td>2 years</td>
<td>7.1</td>
<td>2</td>
<td>&lt;26</td>
<td>x</td>
</tr>
<tr>
<td>2 (F)</td>
<td>A</td>
<td>18 years</td>
<td>3.2</td>
<td>3</td>
<td>&lt;26</td>
<td>x</td>
</tr>
<tr>
<td>3 (F)</td>
<td>D</td>
<td>25 years</td>
<td>3.2</td>
<td>41</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>4 (F)</td>
<td>A</td>
<td>3 years</td>
<td>0.3</td>
<td>14</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>5 (M)</td>
<td>A</td>
<td>11 years</td>
<td>2.6</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 (F)</td>
<td>D</td>
<td>2 years</td>
<td>2.5</td>
<td>&lt;26</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>7 (M)</td>
<td>C</td>
<td>30 years</td>
<td>1.9</td>
<td>23</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>8 (F)</td>
<td>D</td>
<td>5 years</td>
<td>2.5</td>
<td>17</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>9 (F)</td>
<td>A</td>
<td>10 years</td>
<td>2.6</td>
<td>36</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>10 (F)</td>
<td>A</td>
<td>4 years</td>
<td>4.3</td>
<td>37</td>
<td>x</td>
<td></td>
</tr>
</tbody>
</table>

*Tomblin et al., 2002*
Bowel dysfunction is common in chronic neurological illness. Approximately 80% of patients with established spinal injury are constipated\(^1\), and up to 70% of patients with multiple sclerosis report faecal incontinence\(^2\). These symptoms have a huge negative burden on such chronically disabled patients\(^1\). The aetiology and pathogenesis of gut dysfunction in neurological disease is poorly understood\(^3\), but putative mechanisms include:

- loss of voluntary control of striated pelvic musculature
- hindgut sensory and autonomic denervation
- colonic dysmotility (related to enteric neuropathy or patient immobility)
- drug adverse effects
- psychological disturbance related to loss of independence.

Current management is empirical with the principle of a scheduled regular regime being the cornerstone of management. Bowel management has to take account of the specific needs of the patient, taking consideration of attendant availability. The place of drug therapy is to provide predictable elimination of stool, ideally using rectal stimulants rather than laxatives\(^4\). Even in patients with hindgut denervation, behavioural therapies can be profitably employed\(^5\). Surgical methods should be considered for the few patients who are refractory to medical therapy\(^6\). The future holds promise of new therapeutic options. In particular, the advent of enterokinetic drugs and the possibility of direct electrical nerve stimulation offer the potential to treat intractable symptoms in patients with chronic nerve injury.

References

Prevalence of Gut Dysfunction  
Spinal Injury (Glickman and Kamm 1998, St Mark’s)  
115 patients with established spinal injury  
Questionnaire assessment  
• 95% required >1 method to defaecate  
• 50% became dependent on others  
• Perception of problem:  
  • loss of mobility 6.8  
  • bowel dysfunction 5.2  

Management: Behavioural Therapy  
Multiple Sclerosis (Wiesel et al 2000, St Mark’s)  
13 patients (8 female) with MS (median 10 years)  
Constipation + faecal incontinence  
Anorectal physiology pre-treatment  
Median 4 sessions biofeedback  
14 month follow-up  
• 5/13 (39%) improved  
• Predictive factors:  
  • Non-relapsing disease, mild-moderate responsibility, females  
  • No physiological disease predicted outcome  

Future Management: Electrical Stimulation  
Spinal Injury (Chia et al, 1996, Singapore)  
8 patients with spinal injury  
Sacral anterior root stimulators  
Questionnaire assessment and anal manometry  
• 4/8 achieved spontaneous bowel emptying  
• 6/8 improved bowel function  
• Beware autonomic dysreflexia