

# Current perspectives in chronic constipation: a scientific and clinical symposium

**Endorsed by:**

**British Society of Gastroenterology**

**(Neurogastroenterology & Motility Section)**

**Association of Coloproctology of Great Britain & Ireland**

**European Society of Neurogastroenterology and Motility**

## PROGRAMME & ABSTRACTS

**9<sup>th</sup> & 10<sup>th</sup> FEBRUARY, 2009**

**THE GREAT HALL & OCTAGON  
QUEEN MARY UNIVERSITY OF LONDON**

**MILE END, LONDON, UK**



**Barts and The London**  
School of Medicine and Dentistry



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# FACULTY

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## Current perspectives in chronic constipation: a scientific and clinical symposium

### PRINCIPAL ORGANISER

Mark Scott

### COURSE ADMINISTRATION

Jackie Harbour

Sue Surguy

### INTERNATIONAL STEERING GROUP

Ian Cook

Satish Rao

Marc Benninga

### MEMBERS

Qasim Aziz

Simon Brookes

Phil Dinning

Carlo Di Lorenzo

Anne-Marie Leroi

Mario Pescatori

Eamonn Quigley

Harald Rosen

Jan Tack

Bill Whitehead

### LOCAL ORGANISING COMMITTEE

Peter Lunniss

Charles Knowles

Marc Gladman

Jose Behar

Nick Croft

Roberto Di Giorgio

Anton Emmanuel

Peter Milla

Theresa Porrett

Risto Rintala

Terry Smith

Nick Talley

Norman Williams

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Norgine Pharmaceuticals

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B-K Medical Systems

Wiley-Blackwell

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# WELCOME NOTE

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## ***Current perspectives in chronic constipation: a scientific and clinical symposium***

Dear Colleague

On behalf of the organising committee, I would like to welcome you to East London for this two day symposium on chronic constipation. Despite the high prevalence of this condition, and the huge burden this places on healthcare resources (only this month in *Gastroenterology* [2009; 139: 376-86] it is reported that in the US alone in 2004, patients with a primary complaint of constipation were responsible for 6.3 million visits to medical care centres, resulting in total (direct and indirect) costs of \$1.7 billion), it is perhaps somewhat surprising that this is the first major meeting dedicated to this common clinical problem in over a decade. By assembling what I'm sure you'll agree is an outstanding group of speakers, who are recognised authorities in their respective fields, we hope to provide a contemporary view of both scientific and clinical aspects of chronic constipation, and to highlight significant advances that have been made in many areas pertinent to the condition (i.e. pathophysiology, diagnostic assessment and aetiology). A particular focus has been given to management, both in the adult and paediatric patient, with medical, conservative and surgical options all being considered. Nevertheless, it is clear that numerous challenges remain, and we hope to balance the meeting by attempting to recognise 'areas of need', and identifying directions for future research.

Of course, putting on a venture of this size requires considerable planning and organisation, and there are a number of individuals I wish to thank for the time and effort that they have invested. First and foremost, I would like to pay tribute to Jackie Harbour, the Course Administrator, and also Sue Surguy for their tireless hard work. Secondly, I am absolutely indebted to Ian Cook and Satish Rao, and also Peter Lunniss, Marc Benninga and Charlie Knowles for all of their critical comments, their availability (seemingly at all times of the day and night), and for always responding so quickly to the incessant volume of e-mails they each received. Thirdly, I am enormously grateful to all of our sponsors who have contributed so generously in a less than ideal economic climate. I would encourage you all to visit the Exhibitor Stands during coffee and lunch breaks in The Octagon. Finally, we are all thankful to The British Society of Gastroenterology (Neurogastroenterology and Motility Section: Lesley Houghton), The European Society of Neurogastroenterology and Motility (Paul Enck and Fernando Azpiroz) and The Association of Coloproctology of Great Britain and Ireland (Graham Williams) for their endorsement of this event.

We sincerely hope that you enjoy the symposium, and particularly encourage your active participation; there is plenty of opportunity to direct your questions to each of the faculty, and for your involvement in the panel discussions at the end of each session. I am pleased to confirm that the programme is under review for accreditation by the Royal College of Physicians of London for 11 CPD points.

Finally, you will see from this programme that a Round Table Meeting for the faculty members follows the main symposium. This will allow us to re-address many of the contentious issues raised at the main meeting, for potential inclusion in a *Neurogastroenterology and Motility* journal supplement that will consolidate a series of contemporary review articles devoted to the subject of chronic constipation. Publication date is set for August 2009. Please look out for this.

With very best wishes



**Mark Scott**  
Principal Organiser



**S Mark Scott, PhD**  
Senior Clinical Scientist  
Centre for Academic Surgery  
& Neurogastroenterology Group  
Barts and The London  
School of Medicine and Dentistry  
London, UK

# SCIENTIFIC PROGRAMME

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Monday, 9<sup>th</sup> February 2009

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## MORNING SESSION

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**09:30** REGISTRATION AND COFFEE

**10:25** Welcome and housekeeping  
*Peter Lunniss*

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### OPENING ADDRESS

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**10:30** Challenges in constipation  
*Ian Cook*

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### COLORECTAL NEUROANATOMY AND PATHOPHYSIOLOGICAL MECHANISMS: A CONTEMPORARY VISION

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Chairs: *Nick Talley, Peter Lunniss*

**10:45** Neuroanatomical basis of colorectal function  
*Simon Brookes*

**11:05** Colorectal motor dysfunction  
*Phil Dinning*

**11:30** Colorectal sensory dysfunction  
*Marc Gladman*

**11:55** The enteric nervous system in the regulation of colorectal motility: lessons from animal models  
*Terry Smith*

**12:20** PANEL DISCUSSION

**12:35** BREAK – LUNCH  
(Exhibitor Area – The Octagon)

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## AFTERNOON SESSION

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### CONTROVERSIES IN CLINICAL MANAGEMENT

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**DEBATE:** Classification, definitions and diagnostic categories, and valid outcome measures

Moderator: *Satish Rao*

**13:30** Symptom-based?  
*Nick Talley*

**13:50** Measurement-based?  
*Ian Cook*

**14:10** PANEL DISCUSSION  
*Ian Cook, Nick Talley, Bill Whitehead, Jan Tack, Charles Knowles*

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## AFTERNOON SESSION (CONT.)

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Chairs: *Marc Benninga, Marc Gladman*

- 14:30** Which physiological investigations are appropriate?  
*Mark Scott*
- 14:50** What is the spectrum of rectal evacuatory dysfunction?  
*Peter Lunniss*
- 15:10** Dyssynergic defaecation: fact or fiction?  
*Satish Rao*
- 15:30** PANEL DISCUSSION
- 15:45** BREAK – TEA / COFFEE  
(Exhibitor Area – The Octagon)

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## AETIOLOGICAL FACTORS

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Chairs: *Bill Whitehead, Jan Tack*

- 16.10** Secondary causes of constipation: ageing, drugs and neurological disease or injury  
*Anne-Marie Leroi*
- 16.35** Idiopathic constipation: why predominantly women?  
*Jose Behar*
- 16.55** Idiopathic constipation: genetic or environmental?  
*Roberto De Giorgio*
- 17.15** Primary neuromuscular or ICC dysfunction: fact or fiction?  
*Charles Knowles*
- 17:35** PANEL DISCUSSION
- 17:50** Closing remarks  
*Peter Lunniss*
- 17:55** MEETING CLOSE

# SCIENTIFIC PROGRAMME

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Tuesday, 10<sup>th</sup> February 2009

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## MORNING SESSION

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**07:45** REGISTRATION AND COFFEE

**08:25** Welcome and housekeeping  
*Charles Knowles*

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### PAEDIATRIC CONSTIPATION

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Chairs: *Peter Milla, Nick Croft*

**08:30** Pathophysiology and investigation. Do paediatric and adult constipation differ?  
*Marc Benninga*

**08:55** Non-surgical management  
*Carlo Di Lorenzo*

**09:15** Surgical management  
*Risto Rintala*

**09:35** PANEL DISCUSSION

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### MANAGEMENT OF ADULT CONSTIPATION SESSION 1: MEDICAL TREATMENTS

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Chairs: *Ian Cook, Qasim Aziz*

**09:50** The rationale use of laxatives in secondary care  
*Anton Emmanuel*

**10:15** Is there a role for probiotics?  
*Eamonn Quigley*

**10:35** PANEL DISCUSSION

**10:45** BREAK – TEA / COFFEE  
(Exhibitor Area – The Octagon)

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### MANAGEMENT OF ADULT CONSTIPATION SESSION 2: CONSERVATIVE TREATMENTS

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Chairs: *Satish Rao, Mario Pescatori*

**11:10** The role of the colorectal nurse specialist  
*Theresa Porrett*

**11:30** Behavioural therapy, and a critical appraisal of bowel retraining  
*Bill Whitehead*

**11:55** PANEL DISCUSSION

**12:05** BREAK – LUNCH  
(Exhibitor Area – The Octagon)

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## AFTERNOON SESSION

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### KEYNOTE LECTURE

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Introduced by: *Eamonn Quigley*

**13:00**      Evolving and future medical therapies  
*Jan Tack*

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### MANAGEMENT OF ADULT CONSTIPATION SESSION 3: SURGICAL TREATMENTS

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Chairs: *Norman Williams, Anton Emmanuel*

**13.25**      Surgery for severe rectal evacuatory problems: does anything work?  
*Mario Pescatori*

**13.45**      Is there a still a role for colectomy?  
*Charles Knowles*

**14.00**      Sacral nerve neuromodulation: the new frontier in treatment?  
*Harald Rosen*

**14:20**      PANEL DISCUSSION

**14:35**      Closing remarks  
*Mark Scott*

**14:40**      MEETING END

**15:00**      ROUND TABLE FACULTY MEETING  
(Principal's Dining Room)

# BIOGRAPHIES

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**Ian Cook, MBBS (Hons), MD Syd, FRACP  
Sydney, Australia**

Ian Cook graduated with honours in Medicine from the University of Sydney in 1978, and was awarded his Doctorate in Medicine by the University of Sydney in 1989. He completed research fellowships at: McMaster University, Ontario (1985-6); the Medical College of Wisconsin (1987); and the University of Adelaide where he held the Gwendolyn Michell Senior Research Fellowship in Medicine (1988-90). Since then, he has been Director of Gastroenterology and Hepatology at St George Hospital, Sydney. Over the past 20 years he has built up a program of research into gastrointestinal motor disorders with a focus on pharyngo-oesophageal physiology, swallowing disorders, colonic motor function and the pathophysiology of severe constipation. Additional research activities include: investigation of the correlation between symptoms and physiological measures in gut motor disorders; sensory perception and afferent nerve function in the functional gastrointestinal disorders, as well as the evaluation of novel therapies in gastrointestinal disorders. From this research he has published over 120 original peer-reviewed papers, book chapters and review articles.



**Simon Brookes, BSc (Hons), PhD  
Adelaide, Australia**

Simon Brookes has worked extensively on the neuroscience of the organs of the body, mostly on the gastrointestinal tract. He was awarded a BSc (Hons.) from Bristol University in 1980, majoring in psychology and zoology. He followed this with research studies for his PhD (awarded in 1984) on the insect nervous system. This was followed by a post-doctoral research appointment at the Royal London Hospital, studying enteric neurons in the gut wall, which was followed by a research position at Flinders University. This led on to the award of a Senior Research Fellowship in Digestive Science from the Australian Gastroenterology Society in 1992, followed by a National Health and Medical Research Council Senior Research Fellowship in 1997. He has published over 90 research papers, reviews and chapters to date and was appointed in 2005 as Professor and Chairman of the Department of Human Physiology at Flinders University.



**Phil Dinning, BSc (Hons), PhD  
Sydney, Australia**

After completing a BSc (Hons) in Marine Biology in 1993, Phil Dinning found himself accepting a job as research assistant in the Gastroenterology Department of St George Hospital, examining colonic motor function in constipated patients. Fifteen years on, after completing a PhD for his work on "*Relationships between ileocolonic motor patterns and flow in health and in constipation*", he is now the Senior Research Fellow in the same department. He has pioneered techniques to both construct and intubate manometry catheters into the colon and this work was rewarded with publication of the first prolonged pan-colonic motility studies recorded in the unprepared bowel of patients with constipation. This work continues, and in collaboration with the CSIRO Australia, he is developing tools capable of creating high-resolution maps of motor activity throughout the entire colon. In collaboration with Barts and The London School of Medicine and Dentistry, it is hoped these tools will provide far greater insight into the pathophysiology of motor patterns associated with constipation.

# BIOGRAPHIES

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**Marc Gladman, PhD, MRCOG, FRCS (Gen Surg)**  
**London, UK**

Marc Gladman is currently a UKCRC Clinical Lecturer at Barts and The London, Queen Mary's School of Medicine & Dentistry, University of London. His clinical and academic interests relate to sensory dysfunction of the rectum. He was awarded a PhD in 2005 by the University of London for his work on rectal hyposensitivity that was funded by the Frances and Augustus Newman Foundation at The Royal College of Surgeons of England. Currently, he is undertaking a period of post-doctoral research investigating abnormal visceral sensitivity in patients with functional bowel disorders. His principal interests relate to:

- detailed evaluation of anorectal geometric and biomechanical properties and afferent nerve function in patients with functional bowel disorders;
- psychophysiological profiling of patients with abnormal visceral sensitivity;
- *in vitro* electrophysiological recording from rectal afferent neurons and labelling of human afferent neurons to identify their endings within myenteric ganglia

He serves as an Editorial Board member at the journal *Neurogastroenterology and Motility* and is the author of 30 peer-reviewed publications, 10 books and 15 book chapters.



**Terry Smith, BSc (Hons), MSc, PhD**  
**Reno, USA**

Terence Smith is Professor and Director of the Dynamic Imaging Core in the Department of Physiology and Cell Biology, University of Nevada School of Medicine, Reno, Nevada, USA. He was honoured with the Janssen Award (AGA) for excellence in basic research in Digestive Sciences in 2003.

He graduated (1970) with a BSc (Hons.) in Physics, and an MSc in Solid State Physics from the University of Sussex, UK. Following studies in low temperature physics and biophysics, he became a PhD student of Professors Mollie Holman and David Hirst (who first classified enteric AH and S neurons) in the Neuroscience group at Monash University, Australia. Following graduation (1984), he had Post Doctoral Fellowships with Kenton Sanders (Reno) and Marcello Costa and John Furness (Adelaide). He then became an Assistant Professor at the University of Virginia, returning to Reno as an Associate Professor in 1995. The major thrust of his laboratory is the enteric neural control of motility. His group has developed calcium imaging techniques to monitor how enteric neural and ICC networks interact and control propagation of activity within the muscle. They have proposed several paradigm shifts in GI physiology, including: 1) the two muscle layers of the muscularis externa are synchronously (not reciprocally) activated during peristaltic reflexes; 2) there are different functional classes of myenteric sensory neurons; 3) there is muscle tone dependent and stretch dependent peristalsis; 4) colonic accommodation and slow transit result from reflexes triggered by elongation, and 5) faecal matter regulates the propagation of colonic MMCs. He has published over 100 well cited articles in prestigious journals, including *Nature*.

# BIOGRAPHIES

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**Nick Talley, MD, PhD**  
**Jacksonville, USA**

Nick Talley is the Chair of the Department of Internal Medicine at the Mayo Clinic in Jacksonville, Florida. He holds the rank of Professor of Medicine at the Mayo Clinic College of Medicine, and also the rank of Professor of Epidemiology. Dr Talley has joint appointments in the Divisions of Gastroenterology & Hepatology and Epidemiology in Mayo Clinic Rochester and Mayo Clinic Jacksonville. He was formerly Director of the Motility Interest Group in Mayo Clinic Rochester, and before that was the Foundation

Professor of Medicine, Nepean Hospital and the University of Sydney.

Dr. Talley is currently editor-in-chief of the American Journal of Gastroenterology and serves on a number of prominent editorial boards. He is a founding member of the Rome Foundation, a past President of the Functional Brain-Gut Research Group, was a counsellor in the American Gastroenterology Association Motility Section, and serves as a member of the Board of the American College of Gastroenterology. He has a major interest in medical education. His popular student textbook, "*Clinical Examination: A Systematic Guide to Physical Diagnosis*", is in its 5<sup>th</sup> edition and is distributed worldwide. His research is primarily focused on functional disorders, dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori* and eosinophilic disorders of the gut. He has recently described with his team the description of a new disease entity, eosinophilic duodenitis, linked to functional dyspepsia. His group has also documented a genetic component in upper and lower functional bowel diseases. He has published over 500 original and review articles in the peer-reviewed literature, and he is considered one of the leading authorities in clinical research on the stomach. He currently has support from the NIH as Principal Investigator evaluating the pathophysiology and pharmacogenomics of antidepressant therapy in functional dyspepsia.



**Mark Scott, BSc (Hons), PhD**  
**London, UK**

Mark Scott has a BSc (Hons.) in Physiology & Biology, and in 1998 was awarded a PhD in Physiology / Medicine from the University of London for his work on "*Prolonged monitoring of colonic motor activity by an ambulatory recording technique*". He is currently Senior Clinical Scientist within the Centre for Academic Surgery at Barts and The London School of Medicine and Dentistry. He has a long experience, both clinical and academic, related to the physiological investigation of functional gastrointestinal disorders, and was

integral to setting up of the GI Physiology Unit, which he has managed on a day-to-day basis for the past decade. The Unit has an international reputation, and provides a clinical service to >2000 patients per year, which supplies the resources for aligned research; there are currently 20 full-time and affiliated staff members.

Together with Qasim Aziz and Charles Knowles, Mark was central to the founding of the new Neurogastroenterology Group at Barts and The London in 2007. His research interests are focussed on clinical GI (principally colorectal) physiological investigation, and jointly with Peter Lunniss he directs a flourishing research programme involving the supervision of several research fellows. Originating in a fundamental philosophy of carefully phenotyping patients through comprehensive investigation, the group's pioneering work on visceral *hyposensitivity* has gained international recognition. A further principal research interest, particularly through collaboration with Ian Cook and Phil Dinning, concerns assessment of pancolon motor function using novel methodologies. He is author of over 70 peer-reviewed publications, and 8 book chapters.

# BIOGRAPHIES

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**Peter Lunniss, BSc, MBBS, MS, FRCS, FRCS (Gen)  
London, UK**

Peter Lunniss was appointed Senior Lecturer, Centre for Academic Surgery, ICMS, Queen Mary University of London, and Honorary Consultant in General and Colorectal Surgery at Barts and The London, and Homerton NHS Hospitals, London in 1997. His higher surgical training in coloproctology included over 3 years at St. Mark's Hospital, where he gained his MS degree on the subject of anal fistula, and a period as Chief Resident, Mount Sinai Hospital, Toronto, in Professor Zane Cohen's Unit. He is an active Colorectal Surgeon, and is Lead Surgeon at Homerton Hospital in addition to having a (predominantly tertiary referral) clinical practice at The Royal London Hospital. His research is based in the Gastrointestinal Physiology Unit, alongside Dr Mark Scott and Mr Charles Knowles, with emphasis on increasing our understanding of the physiology of continence and defaecation in health, the pathophysiologies associated with faecal incontinence, constipation and rectal evacuatory dysfunction and the effects of interventions; he currently co-supervises 5 research fellows towards higher academic degrees. He is the author of over 70 peer-reviewed journal publications, 26 book chapters and co-editor of one book.



**Satish Rao, PhD, MD, FRCP (Lon), FACG, AGAF  
Iowa, USA**

Satish Rao received his MD from Osmania Medical College, Hyderabad, India, his PhD from the University of Sheffield, UK, and the Fellowship of the Royal College of Physicians (FRCP) in London, UK, in 1997. He completed his training in internal medicine at several academic centres in UK, and a clinical research fellowship in gastroenterology at the Royal Hallamshire Hospital, University of Sheffield. Currently, Dr. Rao is a Professor of Medicine and Director, Neurogastroenterology and GI Motility and Biofeedback Program, Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City.

Dr Rao's research interests focus on the pathophysiology and treatment of IBS, constipation and faecal incontinence and visceral pain, particularly oesophageal chest pain. He has pioneered several new techniques of evaluating oesophageal, gastric, colonic, and anorectal function, in particular the brain-gut axis, has received several patents, and pioneered the technique of biofeedback therapy for dyssynergic defecation and is currently investigating the neurobiologic mechanisms of biofeedback therapy. He is pioneering new treatments for fructose intolerance. He has received numerous awards, and is the only physician to date who has received all 3 meritorious honours from the American Gastroenterological Association (AGA): the AGA Distinguished Clinician Award, AGA Masters Award for Outstanding Clinical Research and the AGA Distinguished Educator Award. In 2005, he also received the American College of Gastroenterology (ACG) Auxiliary Research Award, the highest research award from ACG.

Dr Rao has edited four books, published over 250 articles, and is a reviewer for major international journals. He is a member of several distinguished medical and research societies. He is President elect and serves as Chair, Clinical Practice and Education Committees, American Neurogastroenterology & Motility Society, and an international advisor for the Royal College of Physicians, London, and is on the editorial board of Neurogastroenterology and Motility, Expert Reviews in Gastroenterology and Hepatology, and World Journal of Gastroenterology.

# BIOGRAPHIES

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**Anne-Marie Leroi, PhD MD**  
**Rouen, France**

Anne-Marie Leroi got her MD degree from Rouen University Hospital in France in 1991. She started scientific work on the brain-gut axis as a research fellow in Sherbrooke University in Canada, with Professor Devroede, followed by a period of study with Professor Mike Kamm at St Mark's Hospital in London. After returning to France, she became Professor of Medicine and Human Physiology at Rouen University Hospital in 2000. She became the head of the Physiology Department in 2005. This Department now has 30 employees, 6 doctors, 2 residents and 2 research fellows. It is a centre of functional digestive investigations where tests such as high resolution manometry, impedancometry, breath tests, electrophysiological techniques, 24 hour duodeno-jejunal and colonic manometry, and techniques of magnetic stimulation are performed. She has published several clinical papers in the fields of neurogastroenterology and functional digestive disorders, particularly concerning sacral nerve stimulation (SNS). She leads the SNS club for digestive indications in France.



**Jose Behar, MD**  
**Providence, USA**

Jose Behar is a Professor of Medicine (Research track) at the Warren Alpert Medical School of Brown University. He obtained his fellowship in Gastroenterology at the Boston City Hospital and Harvard Medical School. His major research interests include the study of the pathogenesis of gastrointestinal motility disorders. He has published over 130 original manuscripts in Gastroenterology, American Journal of Physiology, Journal of Pharmacology and Therapeutics and Journal of Biology and Chemistry. He has published a series of manuscripts on 1) the role of cholesterol and bile acids in the pathogenesis of chronic cholecystitis; 2) the role of progesterone receptors in the pathogenesis of slow transit constipation in females and the contribution of COX enzymes and prostaglandins in the genesis of basal colonic motility; 3) in collaboration with Piero Biancani, PhD we are studying the signal transduction mechanisms in the genesis of lower oesophageal sphincter tonic contraction and of phasic oesophageal contractions and the role of acid reflux in the pathogenesis of lower oesophageal sphincter incompetence. We are currently investigating the role of vanilloid receptors (TRPV-1) in the pathogenesis of heartburn and in the development of oesophagitis; 4) in collaboration with Wei Bao Cao, MD we are studying the mechanisms of progression of intestinal metaplasia of Barrett's oesophagus to dysplasia and adenocarcinoma induced by acid exposure. Professor Behar is a member of the American Gastroenterological Association and of the American Motility Society. He has served in several committees in both Societies, organized several symposia on gallbladder disease, colonic and oesophageal disorders. He was the principal investigator of NIH grants to study gallbladder and colonic motility disorders.

# BIOGRAPHIES

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**Roberto De Giorgio, PhD, MD**  
**Bologna, Italy**

Roberto De Giorgio is Assistant Professor of Medicine and Consultant Gastroenterologist (since 2001) at the Department of Clinical Medicine, University of Bologna, Italy. He graduated (MD) from the University of Bologna in 1984, specialty in Internal Medicine and Gastroenterology. He was a postdoctoral fellow at the Center for Ulcer Research and Education / Digestive Diseases Center (CURE / DDC), UCLA, Los Angeles from 1989 to 1993, attended a PhD inter-university program (Verona-Padua-Bologna, Italy, from 1993 to 1996) and was awarded a PhD in 1997. His main research interests are the assessment of changes occurring to the enteric nervous system, ICC and smooth muscle in patients with functional bowel disorders and with severe impairment of gastrointestinal motility. Other research projects are aimed at elucidating the impact of inflammation on enteric neuronal plasticity in different experimental animal models as well as in humans. Roberto is member of several International and National societies (e.g. American Gastroenterological Association, American Neurogastroenterology and Motility Society) and is author and co-author of more than 150 publications in International peer-reviewed journals. He serves as referee for a number of journals e.g. Gastroenterology, Clinical Gastroenterology and Hepatology, Gut, British Journal of Pharmacology, Neurogastroenterology and Motility, Digestive Diseases and Sciences, Digestive and Liver Disease, and is member of the Editorial Boards of Neurogastroenterology and Motility, and Digestive and Liver Disease. He also serves as referee for research grant applications (the International Committee of the Inter-University Project Application, Ministry of Research and Education of Belgium, Wellcome Trust UK, NIH-NSF of USA).



**Charles Knowles, PhD, FRCS (Eng)**  
**Amsterdam, Netherlands**

Charles Knowles undertook his preclinical training at Cambridge University and then moved to the London Hospital Medical College, qualifying in 1992, and passing the FRCS examination (England) in 1996. He was awarded the degree of PhD at the University of London entitled '*Clinical and aetiological studies in slow transit constipation*' in 2000. After successfully completing the final Intercollegiate Specialty Boards Examination in General & Colorectal Surgery, he was appointed Senior Lecturer in Colorectal Surgery on the basis of a prestigious award from HEFCE partnered by Honorary Consultant appointments at Barts and the London and the Homerton University NHS Foundation Trusts. His main clinical interests are in the management of benign coloproctological conditions including complex functional and inflammatory disease. His research interests address: (1) cellular and molecular basis of visceral sensorimotor dysfunction particularly in relation to visceral hypersensitivity and pain, using both *in vivo* and *in vitro* human models; (2) characterisation of GI neuronal ion channels and exploration as targets for autoimmunity in severe primary and secondary gastrointestinal neuromuscular disease (including Chagas' disease); (3) delineation of histopathological techniques for the study and classification of GI neuromuscular disease; and (4) the use of advanced colorectal physiology to guide surgical treatment, in particular the evolving use of neuromodulation. Charles is Chairman of the Whitechapel Society for Gastroenterological research, a committee member of the neurogastroenterology section of the British Society of Gastroenterology, Deputy Clinical Director of the NHS Bowel Healthcare Technology Cooperative, and Chair of a GI neuromuscular disorders international working group. He has published over 50 original research papers, 12 reviews and 5 books.

# BIOGRAPHIES

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**Marc Benninga, PhD, MD**  
**Amsterdam, The Netherlands**

Marc Benninga studied medicine at the University of Amsterdam, The Netherlands. After receiving his Medical degree he worked as a research fellow at the Department of Paediatric Gastroenterology & Nutrition at the Academic Medical Centre (AMC) in Amsterdam with Jan Taminiau and Hans Büller. He performed extensive research on constipation and faecal incontinence in childhood. Subsequently he was trained in paediatrics at the Wilhelmina Children's Hospital in Utrecht, The Netherlands. After his paediatric training, he performed research at The Women's and Children's Hospital, Adelaide with Geoff Davidson and Taher Omari. During his stay in Adelaide his research focussed on maturation of upper gastrointestinal motility in very young infants. In 1999, he became a staff member in AMC and currently he is the head of the Department of Paediatric Gastroenterology & Nutrition. The focus of his current clinical and research work is gastro-oesophageal reflux disease, recurrent abdominal pain, constipation and functional non-retentive faecal incontinence.



**Carlo Di Lorenzo, MD**  
**Columbus, USA**

Carlo Di Lorenzo is Chief of the Division of Pediatric Gastroenterology at the Nationwide Children's Hospital, Columbus, Ohio and a Professor of Clinical Pediatrics at The Ohio State University. He went to Medical School in Italy at the Naples II School of Medicine. He did research fellowships in Brussels, Belgium and at the University of Southern California, where his research interest led him to study gastrointestinal motility in paediatric and adult patients. Dr Di Lorenzo has co-authored the only book on paediatric gastrointestinal motility, and has published more than 120 peer-reviewed original articles and 80 chapters, invited reviews and editorials focused in improving understanding, diagnosis and treatment of paediatric functional and motility disorders. He serves on the Editorial Boards of the Journal of Pediatric Gastroenterology and Nutrition, and Neurogastroenterology and Motility. He has functioned as a grant reviewer for the National Institutes of Health and as abstract reviewer for the AGA, the ANMS and NASPGHAN. He has chaired the Child-Adolescent Committee of Rome III. Dr Di Lorenzo has served on the Council of NASPGHAN. He currently serves on the ANMS Council, is Secretary-Treasurer of the Functional Brain-Gut Group, is a member of the Sub-board of Pediatric Gastroenterology of the American Board of Pediatrics, and is a member of the Functional GI Disorders and Motility Disorders Working Group of the National Commission on Digestive Diseases (NCDD).

# BIOGRAPHIES

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**Risto Rintala, PhD, MD**  
**Helsinki, Finland**

Risto Rintala graduated from Medical School at Helsinki University in 1975. He did his basic surgical training in Jorvi General District Hospital, speciality training at the Surgical Hospital and also Children's Hospital, University of Helsinki. Speciality in General Surgery, 1983 and in Paediatric Surgery in 1994. He was awarded a PhD in 1991, and made Associate Professor in Paediatric Surgery in 1993. He was a Consultant Paediatric surgeon in Children's Hospital, University of Helsinki from 1985 to 1994. From 1995 to the end of 1996, he was Senior Lecturer and Honorary Consultant in Paediatric Surgery at the Institute of Child Health, University of Liverpool and Alder Hey Children's Hospital, Liverpool. He has been Professor of Paediatric Surgery and Chief of Paediatric Surgery in Helsinki since 1997. He is a regular visiting professor and consulting surgeon in 9 Finnish, Scandinavian and Baltic University Hospitals. Scientific activity includes 147 peer-reviewed original publications, 40 book chapters and numerous congress abstracts and invited talks.



**Anton Emmanuel, BSc, MD, FRCP**  
**London, UK**

Anton Emmanuel obtained his medical degree from London University. He is a Senior Lecturer in Neurogastroenterology at University College London, and Consultant Gastroenterologist at University College Hospital and the National Hospital for Neurology and Neurosurgery (Queen Square). Prior to this he was Senior Lecturer at Imperial College and an Honorary Consultant Gastroenterologist at St Mark's Hospital. His clinical work encompasses being director of the GI Physiology Unit at University College Hospital as well as providing a general gastroenterology service. His research includes basic gut neurophysiology and the study of the aetiology and management of functional gastrointestinal disorders of the upper and lower gut. He currently supervises 9 post-graduate research fellows undertaking higher degrees. Laboratory work is undertaken jointly with colleagues in UCL. He is the Secretary of the Neurogastroenterology section of the British Society of Gastroenterology. Research currently addresses the following disease areas: gastro-oesophageal reflux and reflux-induced ENT and chest symptoms; gastroparesis; appetite control and obesity; chronic intestinal pseudo-obstruction; pathophysiology of irritable bowel syndrome; physiology of pelvic floor disorders (constipation and faecal incontinence); gut dysfunction in systemic sclerosis; gut dysfunction in spinal cord injury and multiple sclerosis; colorectal sequelae of radiotherapy; colorectal effects of endometriosis; gut-focussed hypnotherapy and biofeedback.

# BIOGRAPHIES

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**Eamonn Quigley, MD, FRCP, FACP, FACG, FRCPI**  
**Cork, Ireland**

Eamonn Quigley is Professor of Medicine and Human Physiology and a Principal Investigator at the Alimentary Pharmabiotic Centre at the National University of Ireland, Cork, Ireland. He serves as President of the World Gastroenterology Organisation (WGO-OMGE) and the American College of Gastroenterology.

Professor Quigley graduated in medicine from the National University of Ireland, Cork in 1976, and completed his residency in internal medicine at the Western Infirmary and associated hospitals in Glasgow, Scotland. There followed a 2 year research fellowship, leading to an MD degree by thesis, at the Mayo Clinic, Rochester, USA. He served as Lecturer in the Department of Medicine (Gastroenterology) at the University of Manchester at Hope Hospital in Salford, England before joining the faculty of the section of Gastroenterology and Hepatology at the University of Nebraska Medical Center in Omaha in 1986, eventually serving as Division Chief. He returned to University College Cork, his *alma mater*, in 1998 and served two terms as Head of the Medical School from 2000-2007.

His major research interests include motility, functional gastrointestinal disease, neurogastroenterology, gastro-oesophageal reflux disease and probiotics in health and disease.



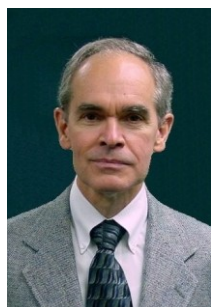
**Theresa Porrett RGN, MSc**  
**London, UK**

Terri was a ward sister at St Mark's Hospital before she joined the Homerton University Hospital NHS Foundation Trust in 1991 as Clinical Nurse Specialist in Stoma Care. She is currently Nurse Consultant in Coloproctology (2001-Present), and Clinical Director of the North East London Bowel Cancer Screening Centre. Terri has been instrumental in developing a range of nurse-led colorectal services for patients at the Homerton. In 2006 the Homerton Colorectal Nursing Department was accredited as an Academic Department of Advanced Colorectal Nursing Practice by City University. Her main area of clinical practice is in benign defaecatory disorders and recent service developments have included an integrated community and acute service Pelvic Floor Dysfunction service.

Terri is currently undertaking a PhD, exploring the coping and help seeking behaviour of women with pelvic floor dysfunction. She is a visiting Lecturer for the Burdett Institute, Kings College London, and City University. Terri has published 2 textbooks embracing all aspects of colorectal nursing practice, and has published extensively in medical colorectal and nursing gastrointestinal journals.

# BIOGRAPHIES

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**William Whitehead, PhD**  
**Chapel Hill, USA**

Dr Whitehead is Professor of Medicine and Adjunct Professor of Gynecology at the University of North Carolina (UNC) School of Medicine. He is co-director of the UNC Center for Functional Gastrointestinal and Motility Disorders. He serves on the NIH Behavioral Medicine Review Panel and the scientific advisory committees of two NIH research networks.

Dr Whitehead received his PhD from the University of Chicago in clinical psychology and physiology in 1973, and did his dissertation research on the biofeedback conditioning of gastric acid secretion. After graduation, he joined the faculty of the Department of Psychiatry, University of Cincinnati College of Medicine. From 1979 to 1993 he was a visiting scientist at the National Institute on Aging and faculty member in the Department of Psychiatry at the Johns Hopkins University School of Medicine. In 1993 he moved to UNC at Chapel Hill to direct the GI Motility Laboratory.

Dr Whitehead has been continuously funded by NIH since 1977. His 36 RO1 grants have included studies of: (1) the causes and treatment of faecal incontinence in special populations such as spina bifida and elderly; (2) the causes and treatment of constipation; (3) treatment of rumination syndrome in developmentally disabled children; (4) the role of visceral perception in irritable bowel syndrome; (5) comorbidity of IBS with other disorders; and (6) psychological and behavioural treatment of irritable bowel syndrome. He has published 250 journal articles, books, and book chapters on these topics.



**Jan Tack, PhD, MD**  
**Leuven, Belgium**

Professor Jan Tack is currently a Head of Clinic in the Department of Gastroenterology, a Professor in Internal Medicine and head of the Department of Pathophysiology at the University of Leuven, and a principal researcher in the Center for Gastroenterological Research at the University of Leuven. He graduated *summa cum laude* in 1987 from the University of Leuven, and specialized in internal medicine and gastroenterology at the same institution. A research fellow at the Department of Physiology at the Ohio State University, Columbus, USA, from 1989 to 1990, he has been a research fellow at the Center for Gastroenterological Research at the University of Leuven since 1990. Professor Tack's research lies in the field of neurogastroenterology and motility, and includes diverse topics such as the pathophysiology and management of gastrointestinal functional and motor disorders (including GORD, functional dyspepsia, gastroparesis, dumping syndrome, chronic constipation and IBS), the physiology and pharmacology of the enteric nervous system, GI hormones and the control of satiation and food intake. He has published more than 280 articles and 35 book chapters on various aspects of scientific and clinical gastroenterology.

Professor Tack has won several awards for Basic and Clinical Research in GI Science. He is Past President of the European Society of Esophagology, President Elect of the International Society for Diseases of the Esophagus, editor of *Neurogastroenterology and Motility*, section editor for *Gastroenterology* and associate editor of *Digestion*. He has served as associate editor for *Gut* and serves or has served as a member of the editorial board of *Gastroenterology*, *American Journal of Gastroenterology*, *Alimentary Pharmacology and Therapeutics*, *Journal of Internal Medicine*, *Bailliere's Clinical Gastroenterology* and *The Japanese Journal of Gastroenterology*.

# BIOGRAPHIES

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**Mario Pescatori, MD, FRCS, EBSQ**  
**Rome, Italy**

Mario Pescatori is Chairman of the Coloproctology Unit of ARS Medica Hospital, Rome, Italy, specialising in general and digestive surgery. He was research fellow to the late Sir Alan Parks, and is a fellow of the Royal College of Surgeons of England (*ad eundem*). He has been accredited in surgical coloproctology by the European board, and is Honorary President of the Italian Society of Colorectal Surgery. He is a member of the Mediterranean Society of Coloproctology, the Eurasian Colorectal Technologies Association, the European board for accreditation in surgical coloproctology, the ASCRS, ESCP and Yugoslavian Society of Coloproctology. He is Editor in Chief of Techniques in Coloproctology, a member of the editorial board of International Journal of Colorectal Disease, and of the advisory board of Colorectal Disease. He has authored approximately 150 indexed publication in international journals, and has lectured at the Mayo Clinic, the Cleveland Clinic, St Mark's Hospital and the London Hospital.



**Harald Rosen, MD, EBSQ**  
**Vienna, Austria**

Harald Rosen studied Medicine at the University of Vienna Medical School and got his specialisation in General Surgery in Vienna and in the Massachusetts General Hospital, Harvard University in Boston, USA. He is Visiting Professor at the Universities of: Belgrade, Yugoslavia; Charité Berlin and Regensburg, Germany; Krakow, Poland; Tromsø, Norway; Alexandria, Egypt; and Doha, Qatar. Dr Rosen has published numerous research papers in highly ranked journals and is a pioneer of dynamic graciloplasty, artificial anal sphincter and sacral nerve stimulation as a new treatment for faecal incontinence.

Dr Rosen was appointed Professor of Surgery by the University of Vienna in 2001, and President of the European Society of Surgery in 2005 when he hosted the Annual Meeting of the society in Vienna. Presently he is clinically affiliated to the St. Vincent Hospital, Vienna.

# ABSTRACTS

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## CHALLENGES IN CONSTIPATION

 **Ian Cook**

In covering the breadth of research from the cell through the biomechanical phenomena and ultimately to the symptoms reported by the constipated individual, this meeting aims to identify and grapple with areas of controversy and doubt and to highlight the challenges facing researchers and clinicians. You will hear state of the art and evidence-based presentations from epidemiologists, immunohistochemists, smooth muscle physiologists, human physiologists and the clinicians and therapists trying to cope with these patients. It will become apparent that all of these experts, by necessity, have to focus on their discipline and in so doing, can at times come up with a perspective quite different to his/her colleagues from adjacent disciplines. This is not to say that one is right and the other is wrong, but it can lead to dogmatism and potentially stifle lateral thinking. Given the overwhelming magnitude and heterogeneity of constipation, the challenge for all of us is to try and embrace and understand all the disciplines and points of view and try and establish relevant connections among these disciplines. For example, novel drugs for constipation have been a long time coming. Before we can design better motility drug targets we have to sort out the marked discrepancy among the neuronal immunohistochemical observations in constipated patients. To do that, we need to provide our histochemists with tissue from better-defined, and more homogenous patient populations in whom we have identified more specific physiological and biomechanical perturbations. In turn, that goal demands better methods of symptom assessment and physiological measurement tools (and novel motor patterns and responses) to identify specific biomarkers within the constipation population. (Perhaps it is unrealistic that this “Holy Grail” will come from the whole human physiologist - perhaps the only truly specific biomarkers will come from the histochemist or the geneticist?) As you will see during this meeting, symptom assessment is a relatively blunt instrument and is frequently a poor discriminator of physiological measures in the intact human. Therefore one has to question the wisdom of over-reliance upon subgroup stratification based on symptoms alone. Similarly, current physiological measurement techniques also fall short of the mark as there exists a great deal of overlap and lack of specificity among physiological measurements in these patients also. We look forward to this meeting with great excitement and hope that it will provide a constructive and critical look at where we are and trigger new collaborations and directions for research.

*“Every great advance in science has issued from a new audacity of imagination”  
(John Dewey)*

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## NEUROANATOMICAL BASIS OF COLORECTAL FUNCTION

 **Simon Brookes**

Motility of the colorectum results from the interaction of the smooth muscle apparatus with intrinsic and extrinsic neuronal circuitry. Nerves and muscle can be strongly influenced by mediators released from mast cells, white blood cells, entero-endocrine cells and other cell types in the gut wall. Here we summarise current understanding of the autonomic and sensory innervation at the cellular level, and speculate on functional implications.

The large bowel is innervated from 4 major sources. The enteric nervous system (ENS), (neurons with somata within the gut wall), contains inhibitory and excitatory motor neurons which directly innervate smooth muscle. Intrinsic sensory neurons detect mechanical and chemical stimuli and intrinsic interneurons control the patterning of motor output. Sympathetic neurons (largely adrenergic, with cell bodies in prevertebral, paravertebral and pelvic plexus ganglia, driven from thoracolumbar spinal outputs) provide largely inhibitory input into the ENS, and excitatory innervation of smooth muscle, particularly in the sphincters. Parasympathetic (largely cholinergic) neurons provide an important excitatory input to the ENS, running from the sacral parasympathetic nucleus of the spinal cord, via pelvic plexus ganglia to enteric ganglia in the rectum, with considerable proximal spread. Extrinsic sensory innervation (both thoracolumbar and sacral) encodes the chemical and mechanical state of the large bowel, evoking sensation and activating extrinsic reflex pathways. Recent studies distinguished several discrete functional types of extrinsic sensory neurons morphologically, anatomically and physiologically. Each conveys specific information about the chemical and mechanical milieu. The rectum is innervated by a large number of low threshold, slowly adapting sacral mechanoreceptors that encode both length and tension in a dynamic fashion. These neurons probably activate the spinal parasympathetic pathways during distension of the bowel. All of the colorectum is innervated by medium-to-high threshold mechano-nociceptors, many with specialized mechano-transduction sites on intramural and extramural blood vessels. These pathways, arising from both thoracolumbar and sacral dorsal root ganglia, respond to both wall tension and length and are also strongly activated by chemical mediators released during ischaemia and inflammation. The work of identifying the full complement of extrinsic pathways to the large bowel is far from complete. However, it is becoming clear that different functional regions of the colorectum receive characteristic patterns of extrinsic sensory, sympathetic and parasympathetic innervation, which play an important role in controlling their function.

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## COLORECTAL MOTOR DYSFUNCTION

■ *Phil Dinning*

A clearer understanding of the pathophysiology underpinning constipation is vital before we can appropriately target new therapies or be able to better predict subpopulations who are most likely to benefit from existing therapies. Despite the fact that colonic manometry was first used over 30 years ago, its unique challenges in conduct and interpretation has meant the technique has some way to go before it can fulfil our expectations. At present, colonic manometric measures or responses are not considered to have real diagnostic value. Nonetheless, a number of phenomena have been described consistently in constipated patients. Further, some novel phenomena and modes of presenting pressure patterns and spatio-temporal relationships are emerging which realistically provide hope that we can rectify this deficiency in the future. There is general agreement that patients with idiopathic slow transit constipation display a reduced frequency of high amplitude propagating pressure wave sequences (HAPC or HAPS) and that these can patients display absent or attenuated responses to a range of stimuli such as a meal, waking or to intraluminal Bisacodyl or i.v. cholinergic stimulation. The absence of some of these responses may imply a colonic enteric neuropathy which, in turn may logically dictate colectomy as a treatment option. However, manometric markers discriminatory of differentiating constipation subtypes or the ability to predict such motor patterns on the basis of symptoms remain unknown or untested. For example, fundamental controlled studies comparing colonic manometric patterns among normal transit, slow transit and evacuation disorders, have yet to be performed. Comparisons among studies in patients of similar pathophysiology and symptomatology are difficult because of the lack of standardisation of methodology and measurement definitions. Finally technical constraints have tended to limit both the extent of colon examined and spatial resolution of pressure recordings. Therefore much of the existing data is derived from sites distal to the mid colon, thereby leaving the motor activity of the ascending colon largely undefined. The current evidence derived from colonic manometric studies is reviewed; the shortcomings and strengths of the technique compared and the gaps in our knowledge and future direction of pan-colonic manometry are discussed.

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## COLORECTAL SENSORY DYSFUNCTION

■ **Marc Gladman**

Together with abnormal colonic motility and outlet obstruction, colorectal sensory dysfunction has been proposed as an important underlying pathophysiological mechanism for the development of constipation. However, there have been few direct studies of diminished visceral sensitivity documented in constipated patients, with most limited to the study of impaired rectal sensitivity. Such 'rectal *hyposensitivity*' (RH) relates to a diminished perception of rectal distension and is diagnosed during anorectal physiological investigation. RH appears to be common in patients with constipation, being present in approximately 30% of patients with constipation-predominant irritable bowel syndrome and up to one-quarter of patients with chronic constipation, where it is the only apparent abnormality on physiological testing in many patients. Furthermore, the combination of diminished perception of rectal distension and incomplete evacuation of rectal contents appears to play a significant role in the pathogenesis of faecal seepage / soiling in constipated patients.

Currently, the aetiology of RH is unclear, although there is limited evidence to support the role of pelvic nerve injury, and abnormal toileting behaviour. In current clinical practice, RH is usually diagnosed on the basis of elevated sensory threshold volumes during balloon distension. Traditionally, it is considered that diminished perception of rectal distension in such patients reflects impaired afferent nerve function. However, sensory assessment using balloon distension may not accurately reflect the function of visceral afferents under certain circumstances, since sensory threshold volumes may also be influenced by structural and / or biomechanical properties of the rectum. Indeed, it has recently been shown that diminished perception of rectal distension may occur due to afferent nerve dysfunction in one-third of patients with RH, but is secondary to abnormal rectal structure or biomechanics in the remaining two-thirds.

The optimum treatment of patients with RH is yet to be established. The majority are managed symptomatically, although 'sensory retraining biofeedback' appears to be the most effective treatment, at least in the short-term, and is associated with objective improvement in rectal sensory function. Currently, fundamental questions relating to the contribution of this physiological abnormality to the development of functional bowel disorders remain unanswered. Acknowledgment of the potential importance of RH is thus required by clinicians and researchers to further determine its relevance in management strategies of patients with constipation.

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## THE ENTERIC NERVOUS SYSTEM IN THE REGULATION OF COLORECTAL MOTILITY: LESSONS FROM ANIMAL MODELS

■ *Terry Smith*

Functions of the large bowel include the recovery of water and electrolytes from waste matter that leads to stool formation and storage. To perform these functions, transit through the human colon is slow (>30 hours) compared to that in the small intestine (2 – 4 hours). Our recent studies suggest that a powerful intrinsic “occult” reflex is likely to be a major mechanism underlying colonic storage and slow transit. To discuss this reflex, it is necessary to describe a number of intrinsic sensory neurons in the large bowel.

The reason for the several classes of ascending and descending interneurons in the large bowel was unclear. Our recent studies in the guinea-pig distal colon suggest that in addition to AH sensory neurons (intrinsic primary afferent neurons: IPANS), distinct interneurons in the large bowel are also mechanosensory and respond to either circumferential stretch or longitudinal stretch. AH neurons, which are activated by muscle tension and contraction and stimuli arising from the mucosa, appear to generate muscle tone-dependent peristaltic waves. However, following Nifedipine (1  $\mu$ M) to paralyze the muscle, circumferential stretch evokes a more rapid form of peristaltic activity generated by stretch-sensitive ascending and descending interneurons, since in these preparations without muscle tone, AH neurons are electrically silent. Thus the large bowel has neurons that register muscle tension and stretch, analogous to Golgi tendon organs and muscle spindles in the somatic nervous system.

In addition, we have described a powerful intrinsic, inhibitory “occult reflex” (hidden from view) that is activated in a graded manner by colonic elongation that appears to underlie colonic accommodation and slow transit. This reflex is physiological since when the guinea-pig colon is full of pellets it is normally elongated and pellet propulsion and muscle tone are substantially reduced. Colonic elongation inhibits colonic motility by activating mechanosensitive descending nNOS +ve interneurons that release nitric oxide (NO) to suppress activity in neurons underlying peristaltic (and secretomotor) reflexes, rather than producing a direct output to the muscle. This reflex also occurs in both the guinea-pig rectum and monkey sigmoid colon. Clinically, the intrinsic occult reflex may provide a negative feedback that would contribute to the inhibition of motility associated with constipation in an impacted colon. Significantly, a number of reported changes in slow transit constipation that include an increase in myenteric nNOS neurons, an increase in NO production, a decreased muscle tone and peristalsis, increased absorption and an elongated colon likely affect the occult reflex. Conversely, in animal models of colitis the colon is shortened, NO activity is reduced and enteric neurons are more excitable, suggesting that the occult reflex is disarmed leading to soft stools.

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## CLASSIFICATION, DEFINITIONS AND DIAGNOSTIC CATEGORIES, AND VALID OUTCOME MEASURES

### SYMPTOM-BASED?



***Nick Talley***

Chronic constipation results in a substantial number of consultations in primary care facilities and in specialty practice. However, the definition of chronic constipation still varies widely in the literature, and there is potentially a disconnect between patients and physicians perception of this condition. Chronic constipation has generally been categorized into three broad subgroups based on physiological testing (the gold standard), namely slow colonic transit constipation, normal colonic transit constipation, or defaecation (outlet) disorders. While therapeutic strategies do differ among the subgroups of chronic constipation, and hence identifying subgroups is clinically relevant, symptom-based criteria have not provided a robust discrimination of the physiological subgroups of constipation. These findings may be explained by relatively small sample sizes and inadequate assessments of symptoms. On the other hand, factor analysis generally does not support different subsets. The current Rome III criteria for functional constipation rely on both symptoms and objective testing, and hence the epidemiology of constipation subgroups is very poorly understood. In this presentation, the evidence supporting symptom-based criteria for distinguishing slow transit and pelvic floor dysfunction is critically reviewed.

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## MEASUREMENT-BASED?

 **Ian Cook**

Defining subcategories of constipation is important as it focuses and systematises aetiological, pathophysiological and epidemiological enquiry; and has the potential to dictate logical and cost-effective investigative algorithms for clinicians, to influence management and predict therapeutic outcome. To some extent the current subclassification of constipation goes part way to achieving these aims. However, the fact that we are having this “debate” highlights how far the current classification strategies fall short of the mark. There are many reasons for this shortfall. A subset of normal transit constipation, also without identifiable evacuatory dysfunction, exists for which symptoms can be only partly accounted for by psychobehavioural factors. Constipation is not only heterogeneous but very substantial overlap exists between the delayed colonic transit and pelvic floor dysfunction. Even within the category of pelvic floor dysfunction, a wide range of anatomical abnormalities as well as aberrant neuromuscular responses, are reported – all of which are also found in a substantial proportion of healthy asymptomatic individuals. In some cases this overlap is fortuitous, and in others it may be causal. There is a real need to establish the utility of available and emerging physiological measures. It can be argued that objective measurements for which we have defined normal ranges can obviate the need for unnecessary and invasive investigation or treatments (e.g. colectomy). Indeed, defining a “normal” test may be more relevant than an abnormal test in some circumstances (e.g. transit measurement helps improve the specificity of patient selection by segregating those in whom reports of stool frequency are unreliable). This review evaluates the strength of evidence supporting the reliability, validity, diagnostic accuracy, and clinical utility of the commonly used measurement techniques. The difficulty in evaluating validity and diagnostic accuracy is the need for a “gold standard” against which the test is compared. In lieu of a diagnostic biomarker there are very real problems comparing one (imperfect) test against another. The studies that evaluated the clinical utility of physiological tests, are lacking in most or all of the desirable criteria necessary to achieve their aim (i.e. not prospective, inadequately powered, without prospectively defined and validated primary treatment outcome measures and non-standardised definitions of positivity; non-randomised and nor placebo-controlled). Nonetheless, some data do exist which indicate demonstration of pelvic dyssynergia is predictive of response to biofeedback. The predictors of response to surgery remain far less certain.

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## WHICH PHYSIOLOGICAL INVESTIGATIONS ARE APPROPRIATE?

 **Mark Scott**

Rigorous laboratory assessment of colorectal / anorectal function is not required for all patients with constipation. However, those patients in whom empirical conservative measures have failed, and co-existing disease has been excluded, should be considered for further specialist investigation. As the process of defaecation depends upon multiple and complex physiological (and psychobehavioural) mechanisms, the pathophysiology of constipation is often multifactorial. Assessment should thus be carried out in the context of a *global* evaluation, aimed at both morphology / anatomy and function. The former can be evaluated by physical examination, but in more detail by imaging (static or dynamic), and the latter by clinical history and examination, but in more detail by tests of physiology. Judicious use of these tests is recommended, but in those patients in whom investigation is warranted, a comprehensive and structured assessment should be performed, which aims to address all understood and measurable components which may contribute to the presenting disorder(s) – remember, faecal incontinence frequently coexists, and may be secondary to constipation. However, a fundamental consideration is: even if tests are available (many), are they appropriate (few), and even if they are appropriate, are they practicable in a high volume clinical setting?

Given that the pathophysiology of constipation is generally considered to be an interplay between colonic dysmotility, rectal evacuatory dysfunction and altered rectal sensation (hyposensitivity), a critical appraisal of tests of *colonic transit* (radio-opaque marker studies; scintigraphic techniques; radio-telemetric capsule devices); *the process of defaecation* (evacuation proctography in its many guises, be it X-ray, MRI or scintigraphy vs. balloon expulsion and manometric indices); and *rectal sensory function* (balloon distension vs. barostat) will primarily be addressed. In addition, the utility of other tools such as colonic manometry, ultrasound, and investigations of upper GI function in those individuals with symptoms suggestive of a diffuse pan-enteric motility disorder will be covered. Furthermore, the clinical impact of such investigations will be considered; several studies have demonstrated that the information provided markedly improved diagnostic yield and directly influenced or altered the management plan in a significant proportion of cases. However, there are major limitations which will be highlighted, not least the lack of uniform standardisation of tests, which means that results between centres are often difficult to compare. In addition, robust normative data for all measures of function remain inadequate, particularly with regard to age and gender stratification. Other areas for future progress and research will also be identified; in a complex biological system, measures are usually taken in isolation, and there is thus a need for an integrated approach to investigation, and also the development of newer, well-validated tests that are minimally invasive, physiological, and simple to perform and interpret.

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## WHAT IS THE SPECTRUM OF RECTAL EVACUATORY DYSFUNCTION?

 **Peter Lunniss**

Rectal evacuatory dysfunction is one of many terms embracing symptoms or symptom complexes which result in an individual's dissatisfaction with their evacuatory ability. Its prevalence, as defined by Rome criteria, among Western adult populations, is about 8 – 11%, is more common in women, and affects all ages. Our limited understanding of pathoaetiology results in the distinction between functional (behavioural), pathophysiological and organic bases to symptoms being unclear. This necessarily limits the utility of the Rome classification which is further compromised in acknowledging only dyssynergic defaecation or ineffective evacuatory effort as causes of 'obstructed defaecation' or 'outlet delay'. Furthermore, our investigatory armamentarium is largely confined to the assessment of artificial defaecation in a laboratory setting, rather than spontaneous, natural defaecation. A behavioural basis, reflected by evidence of dyssynergia at attempted (simulated) defaecation is thought to underlie constipation in both childhood and early adulthood, but in whom evidence is mounting of coexistent disturbances to rectal physiology and large bowel sensorimotor function, most dramatic in those with 'idiopathic' megarectum. In others, the problem appears to be one of ineffective defaecatory dynamics, reflected by an inadequate increase in intra-rectal pressure during attempted evacuation. Our ability to assess anatomical changes during evacuation, by a variety of techniques, has resulted in the attribution of rectal evacuatory symptoms to various observed abnormalities (originating in pelvic floor / supporting structure weakness) which are perceived to be associated with obstruction to outflow (rectal intussusception, enterocoele) or evacuatory force dissipation (rectocoele, ballooning perineum). Robust normative data are however lacking, and the coexistence of multiple confounding factors may partly explain symptom continuation despite anatomical correction. The cause / effect relationship between evacuatory dysfunction and colonic motor dysfunction has yet to be fully elucidated. Pancolonic manometry has revealed both attenuated colonic propulsive activity preceding attempts at evacuation and a disassociation between defaecatory urge and propagating colonic activity in those with normal transit but with 'functional' evacuatory dysfunction, and scintigraphic assessment of colonic transit in those with slow transit constipation, with or without marked rectal evacuatory dysfunction, has revealed very similar patterns of delay.

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## DYSSYNERGIC DEFAECATION: FACT OR FICTION?

 **Satish Rao**

Dyssynergic defecation accounts for 30 – 40% of patients with chronic constipation. It significantly affects QOL and psychological behaviour of these subjects. This acquired behavioural problem is due to the inability to coordinate the abdominal and pelvic floor muscles to evacuate stools. These patients demonstrate paradoxical anal contraction, impaired push effort or inadequate anal relaxation or a combination. Nearly 50% of patients have rectal hyposensitivity and over 60% have coexisting slow colonic transit. Recent studies of cortical evoked potentials from the anus and rectum have provided invaluable insights regarding the bidirectional interactions of the gut-brain axis in subjects with dyssynergia. Although most patients with dyssynergia have constipation as the predominant symptom, dyssynergia has also been described in patients with faecal seepage, patients with solitary rectal ulcer syndrome and faecal incontinence.

Today, it is possible to diagnose dyssynergic defecation through a combination of symptom patterns, prospective stool diaries, and anorectal physiological tests. Diagnostic criteria require both the presence of symptoms of constipation and the fulfilment of objective criteria based on anorectal manometry / EMG and balloon expulsion test or colonic transit test or defaecography. Although supportive therapy and laxatives are helpful, by themselves they are ineffective. Recent randomized controlled trials have convincingly shown that neuromuscular training (biofeedback therapy) is superior to sham biofeedback training or laxatives and that this improvement is due to alterations in dyssynergia, sensory function and colonic transit. Also, preliminary studies have revealed that dyssynergics have impaired ano-cortical and recto-cortical evoked potentials, suggesting impaired gut-brain afferent neuronal function. Whether biofeedback therapy improves brain-gut dysfunction merits further appraisal. Long term efficacy has also been demonstrated for neuromuscular training. Development of user-friendly approaches to biofeedback therapy and use of home biofeedback programs and reimbursement for this procedure will significantly enhance the adoption of this treatment by gastroenterologists and colorectal surgeons, and thereby improve care for these patients.

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## Notes

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## SECONDARY CAUSES OF CONSTIPATION: AGEING, DRUGS AND NEUROLOGICAL DISEASE OR INJURY

■ **Anne-Marie Leroi**

Constipation is a common problem in the elderly. Prevalence ranges from 15% to 20% in a community-dwelling elderly population, and up to 50% in some studies of nursing home residents. In these patients, constipation is multifactorial and results from a combination of risk factors, such as reduced fibre and fluid intake, decreased physical activity, and chronic illness, particularly depression, hypothyroidism or neurological disease. Furthermore, drugs which are more often prescribed with increasing age may produce constipation. For example, Codeine – in its various combinations – is widely used as an analgesic for minor muscular and joint pains. Preparations with anticholinergic effects (tricyclic antidepressants and phenothiazines) are all constipating and are also commonly prescribed to elderly people. Moreover, constipation is often associated with disease of the nervous system. Indeed, bowel problems are observed to be the cause of much anxiety and may alter quality of life in the same way as motor disorders. Both central and peripheral neurological lesions are frequent causes of constipation, in which at least two different pathophysiological mechanisms may be involved:

- 1) slow transit constipation due to increasing non-peristaltic motility of colon (inhibited by sympathetic innervation) or due to a decreasing peristaltic motility (activated by parasympathetic innervation);
- 2) a distal constipation due to an outlet obstruction that appears as a side-effect to anorectal sensorimotor disturbances such as reduced anorectal sensibility, anal hypertonia and recto-anal (striated) sphincter dyssynergia.

Impairment of the postprandial colonic response has also been described in patients with spinal lesions or with diabetes mellitus. Parkinson's disease has a particular feature, in that as well as paradoxical contraction of the external sphincter during defaecation due to supra-spinal lesions, there is a loss of dopaminergic neurons in the enteric nervous system. This may explain why patients with Parkinson's disease often suffer from constipation and prolonged colonic transit time. It can therefore be concluded that understanding the very mechanisms of constipation could influence the choice of an appropriate treatment.

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## IDIOPATHIC CONSTIPATION: WHY PREDOMINANTLY WOMEN?

■ *Jose Behar*

There is a lopsided prevalence of idiopathic slow transit constipation (STC) in females (F:M 9:1) and in irritable bowel syndrome (IBS) with predominant constipation of F:M of between 3 and 5:1. This contrasts with a F:M ratio of 1:1 in IBS with predominant diarrhoea. This high prevalence of constipation in females suggested that sex hormones are involved in the pathogenesis of this entity. Progesterone is proposed as one of the factors responsible for the high female prevalence because it: impairs the contraction of colon muscle strips and cells from animals and humans; the high incidence constipation during pregnancy; the transit time being longer during the luteal than in the follicular phase of the menstrual period; and, the phase 3 of the migrating motor complex is slower in females than in males. However, females with STC have normal serum levels of progesterone. These findings suggested that colon muscle cells are more sensitive to these normal progesterone levels.

We examined the effect of progesterone on normal muscle cells and whether similar abnormalities were present in colon muscle cells from women with severe STC compared to females without constipation. Progesterone ( $10^{-5}$  and  $10^{-6}$  M) impaired the contraction induced by CCK-1, ACh and GTP $\gamma$ S (a direct G protein activator). However the contraction induced by Diacylglycerol and Inositol trisphosphate, that bypasses receptors and G proteins, was normal. Progesterone also reduced the mRNA and protein expression of Gq/11 protein and up-regulated the mRNA and protein expression of Gs protein. Progesterone lowered the mRNA and protein expression of COX-1 and TxA2 levels; up-regulated COX-2 and PGE2 levels involved in the maintenance of basal colonic motility. Similar abnormalities were found in muscle cells from females with STC compared to controls. We examined whether progesterone receptors were over-expressed since physiological levels of progesterone ( $10^{-7}$  M) had no effects in normal muscle cells. Progesterone receptor mRNA and protein expression were over-expressed in STC compared to controls suggesting that they were hypersensitive to normal levels of this hormone. The over-expression of progesterone receptors renders these normal muscle cells more sensitive to lower progesterone concentrations responding to concentrations of  $10^{-7}$  M.

Future research studies will determine: 1) whether progesterone receptors are over-expressed in colon epithelial cells so that they can be determined in larger number of patients in mucosal biopsies; 2) whether the over-expression of progesterone receptors in epithelial cells affect SERT-5-hydroxytryptamine levels to explain conflicting reports in patients with IBS-C.

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## IDIOPATHIC CONSTIPATION: GENETIC OR ENVIRONMENTAL?

■ **Roberto De Giorgio**

Constipation affects 2 – 28% of the general population (with a female gender predominance) and represents a considerable burden for society because of direct and indirect costs. Constipation ranges from mild to moderate, up to severe, difficult to treat and debilitating forms. This summary will deal with some pathophysiological aspects of patients with severe chronic constipation, i.e. slow-transit constipation / colonic inertia (STC / CI). Although most cases of STC / CI can be secondary to numerous systemic diseases (e.g. Parkinson's disease), other cases are idiopathic in origin. Any injury affecting the morpho-functional integrity of enteric muscles, interstitial cells of Cajal (ICC) or nerves (either enteric / intrinsic or extrinsic) may lead to a markedly delayed colonic transit as identified in patients with STC / CI. A variety of mechanisms, e.g. genetic and environmental factors, may be responsible for enteric neuro-ICC-muscular abnormalities. Understanding genetics would help with disease etiology and response to therapy. However, apart from some genetic polymorphism found in constipation-predominant IBS, no gene mutations have been identified in STC / CI. Hirschsprung's disease, an extreme form of STC, is characterized by a number of genetic abnormalities (*RET*, *EDNRB*) leading to enteric aganglionosis mainly in the distal bowel. Genetic abnormalities (e.g. *SOX10*, *POLG*) and a locus mapped on chromosome 8, have been demonstrated in patients in whom constipation is due to a diffuse impairment of gut motility, i.e. neurogenic chronic intestinal pseudo-obstruction. *ECGF1* mutations have been shown in MNGIE, a mitochondrial cytopathy characterized by severe digestive symptoms including constipation. Among environmental factors, autoimmunity (cell- and humoral-mediated) and infectious agents (neurotropic viruses) may play a role in severe motility disorders, including STC / CI. Inflammatory / immune-mediated changes targeting the myenteric plexus (hence myenteric ganglionitis) of the colon have been reported in specimens of patients with STC / CI suggesting the role of immune activation in neuronal dysfunction and degeneration. In addition to cellular autoimmunity, patients with STC may have circulating auto-antibodies blocking ion channels, receptors or other intracytoplasmic molecules expressed by neurons, ICC and / or smooth muscle cells. Although the etiology of myenteric ganglionitis remains undetermined, the demonstration showing herpes virus DNA in the myenteric plexus of patients with severe dysmotility raises the exciting possibility that infectious agents can be involved in the pathogenetic cascade leading to inflammatory damage of enteric neurons. In conclusion, despite growing knowledge in this area, research efforts are needed to unravel the basic pathophysiological mechanisms underlying STC / CI. Hopefully this knowledge will help to develop new and effective therapeutic strategies for chronic constipation.

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## PRIMARY NEUROMUSCULAR OR ICC DYSFUNCTION: FACT OR FICTION?

 **Charles Knowles**

Within patients with severe constipation, especially those with physiologically-defined slow-transit constipation, there is some evidence that a histologically-evident structural cause for disease may be present <sup>1</sup>. At a time when surgical resection was more popular than now, the availability of full-thickness colonic tissue led to several studies attempting to identify the presence of enteric neuropathy, myopathy and mesenchymopathy by a variety of methods. On the basis of routine and silver staining, a plethora of studies eluding to the presence of varying degrees of degenerative neuropathy pervaded the literature in the late 1970's and 1980's, with those employing immunohistochemistry following in the 1990s; in parallel were those demonstrating histological changes in the muscularis propria, although these were much fewer. With the realisation of the key role of interstitial cells of Cajal (ICC) in gastrointestinal motility, changes in number and morphology of ICC have become the basis of several studies in the last decade.

Such findings do however require critical appraisal. Extraordinary variability exists in current histopathological techniques used for the study of tissues from patients with suspected GI neuromuscular diseases with wide differences in methodologies and expertise continuing to confound the significance and reliability of a variety of reported histopathological changes in terms of clear delineation from normality, specificity for, and / or causation of disease. Although there have been many studies published from experts in the field, most have their own favoured protocols and techniques, which may be inaccessible or impractical for general pathology laboratories. Whilst some report widespread agreement for a particular methodology, published consensus in this area does not exist and is the subject of an international working group <sup>2</sup>. With the advent of new minimally invasive techniques to safely acquire full-thickness colonic biopsies, these issues require urgent attention, particularly when some treatments may also be guided by histological findings. In this session, the results of studies on constipation are critically discussed in the context of these methodological limitations.

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## PATHOPHYSIOLOGY AND INVESTIGATION. DO PAEDIATRIC AND ADULT CONSTIPATION DIFFER?

■ **Marc Benninga**

Constipation is a very common condition in the general population, both in adults and in children. The prevalence in children ranges from 0.7% to 29.6% with some studies reporting a higher number of constipated boys compared to girls and others report no difference between genders.<sup>1</sup> In adults, constipation affects between 2% and 28% of the general population.<sup>2,3</sup> In contrast with constipated children, available literature suggests a higher prevalence in women than in men.<sup>4</sup> Individuals of lower social, economic and educational level have a tendency towards higher constipation rates. A Swedish prospective cohort study in 8,341 2 – 5 year old children showed that low maternal educational level was significantly associated with constipation.<sup>5</sup>

More than 90% of infants and toddlers present with hard to rock-hard stools,<sup>6</sup> of which 27% are bloody stools. Parents report that 42% of these young children cry and scream when passing these hard stools. Faecal incontinence is the main clinical characteristic in children between the age of 4 and 12 years.<sup>7</sup> This involuntary leakage of faeces may occur several times a day and in some severe cases with large rectal impaction it may also occur at night. Between 10 – 70% of children with constipation complain of non-specific abdominal pain. The majority of constipated children have palpable abdominal masses and / or faecal impaction of the rectal on physical examination. Symptoms in adolescents with constipation differ from those typically found in (young) children.<sup>8</sup> Adolescents less commonly complain of faecal and urinary incontinence. Furthermore, the effect of a high fibre diet or biofeedback is often helpful in adolescents but not in children.

In infants and toddlers, withholding behaviour plays an important role in the development and / or persistence of functional constipation. Several reasons may lead to stool withholding behaviour in infants and children: 1) previous experience with painful or hard stools; 2) anal fissures; 3) lack of time for regular toileting; 4) resistance to use toilets other than the child's own; 5) stressful events; and 6) concurrent illness. Retained stools become progressively more painful and difficult to evacuate leading to even more fear and avoidance of defaecation. Long-term faecal impaction eventually might lead to a dilated rectum with decreased rectal tone and decreased rectal contractility contributing to delayed evacuation of feces.<sup>9</sup> Normal rectal sensation, but higher distensibility (compliance) of the rectum was found in constipated children compared to healthy children.<sup>9</sup> This finding suggests that the rectum is stretched and larger stool volumes are needed to trigger rectal sensation, such as the urge to defecate. A recent study however showed that increased rectal compliance was still found in almost half of the recovered adolescents, indicating a limited role of disturbed rectal compliance in therapy-resistant functional constipation.<sup>10</sup>

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## NON-SURGICAL MANAGEMENT

 **Carlo Di Lorenzo**

Treatment of chronic childhood constipation is typically divided into three stages: disimpaction, maintenance therapy, and monitoring. The most important goal in the treatment of children with constipation is to obtain evacuation of stools without pain. Disimpaction by the oral route, rectal route, or a combination of the two has been shown to be effective. Disimpaction by the oral route is non-invasive and allows for empowerment of children in managing their problem. Even though disimpaction is faster via the rectal approach, such intervention is invasive, emotionally draining, and at times very difficult for families to administer. The choice of treatment is best determined after discussing the options with the family and child. Once the impaction has been removed, the focus of treatment is to prevent re-accumulation of stool (maintenance phase). This is usually achieved by a combination of dietary and behavioural modifications, and pharmacological interventions.

### *Diet*

Increase in juice intake is particularly helpful in children under the age of one. The beneficial effect of dietary fibres for the treatment of childhood constipation is controversial. The role of cow's milk intolerance as an underlying cause of chronic constipation in children has been proposed. In a double-blind, crossover study comparing the effect of 2 weeks of either cow's milk or soy milk in children with constipation, the majority of those receiving soy milk, and none of the children receiving cow's milk improved. Based on these findings, it was suggested that it may be appropriate to place young children with constipation on a 2 week elimination of dietary milk. The role of probiotics in the treatment of childhood constipation is currently under investigation

### *Behavioural interventions*

In a randomized, controlled study evaluating the effect of adding biofeedback to conventional therapy in children with or without anismus, there was no difference in outcome between the two groups after one year. Other behavioural interventions have been shown to add little benefit to standard medical treatment of childhood constipation. The use of more formal psychotherapy has not been evaluated in children although an intriguing pilot study suggested that playing with clay (a brown, messy material that could be construed as a metaphor for faeces) led to symptom resolution in some children.

### *Pharmacologic treatment*

Laxatives are given throughout the maintenance phase in order to assure daily painless bowel movements. Long term success has been reported with both lubricant laxatives and osmotic laxatives. Decisions on which laxative to use is based on a combination of safety, cost, child's choice, ease of administration, and the treating physician's preference. Recent studies performed in children, especially using PEG, will be discussed.

### *Other interventions*

There is evidence that intra-sphincteric injection of *Clostridium botulinum* toxin A is beneficial in children with the diagnosis of anal achalasia. Transcutaneous electrical stimulation (interferential stimulation) has also been used with some encouraging preliminary results in the treatment of severe cases of childhood constipation.

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## SURGICAL MANAGEMENT

### **Risto Rintala**

Constipation is one of the most common paediatric conditions leading the parents of a patient to seek medical help. Reported incidences of constipated patients in general paediatric services range between 3 – 7% and in paediatric gastroenterological services up to 25%. Constipation is also a major cause of faecal incontinence in children. A common belief has been that constipation disappears when the patients go through puberty; however, a recent large study showed that symptoms persist into adulthood in 30% of cases .

The vast majority of children with chronic constipation improve by appropriate medical therapy or with time. In patients with refractory constipation it is mandatory that organic causes of constipation are ruled out. Hirschsprung's disease usually presents early during the first days or weeks of life and the clinical picture is usually different from idiopathic constipation. More subtle forms of ganglion cell abnormalities, that may need to be ruled out include internal sphincter achalasia, hypoganglionosis and intestinal neuronal dysplasia.

There are very few controlled studies in children that are devoted to the surgery of pediatric idiopathic constipation. The MACE procedure that has been originally used for neuropathic incontinence or incontinence following management of anorectal anomalies has been successfully used also for idiopathic constipation. Significant improvement has been reported by several authors in all types of constipation. The MACE procedure can be easily reversed which may make it an attractive alternative for enemas and laxatives especially for pubertal and adolescent patients. Anal dilatations have an established role in the treatment of refractory constipation in children. A recent randomized controlled study, however, did not show any benefit from anal stretch. Internal sphincter myotomy / myectomy has also been used in patients with recalcitrant idiopathic constipation. In a recent randomized study, myectomy and Botox were found equally effective in intractable idiopathic constipation. Colostomy has been used in selected patients with significant patient and parent satisfaction. In paediatric populations, there are no controlled studies on colonic resections for idiopathic constipation and megacolon. High incidences of recurrent constipation have been reported in children who have undergone partial colonic resection. Colectomy and ileo-rectal anastomosis is an option for severe slow transit constipation also in children but systematic reports are lacking. Sacral nerve stimulation is a new successful modality to treat dysfunctional elimination of urine and faeces in adults. A few promising preliminary results have been reported also in children.

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## THE RATIONALE USE OF LAXATIVES IN SECONDARY CARE

■ **Anton Emmanuel**

Only about 4% of community-dwelling patients with constipation are seen in secondary care, and these are usually those with more severe complaints. Lifestyle and behavioural interventions are generally recommended first-line approaches, albeit with limited evidence of clinical benefit to date. Most patients have already tried and failed a high-fibre diet (which is held to optimise stool consistency) by the time they are seen in secondary care. This is not worth repeating as it may exacerbate symptoms in slow-transit constipation and rectal evacuatory dysfunction (symptoms sub-groups who are disproportionately represented in the population referred to secondary care).

The evidence base for stimulant laxatives, stool softeners and osmotic agents is generally of low quality. As such, the onus is on tailoring treatment according to individual symptoms and social factors. The PEG-based osmotic laxatives have been well studied and short-term studies have shown some beneficial effect in stool frequency, but with frequent adverse effects and little improvement in the common constipation-associated symptoms of bloating and colicky pain. Stimulant laxatives are helpful when used on an as-required basis, but again may exacerbate colic and be unpredictable in their action.

Newer agents have been developed in the context of large clinical investigation programs. Tegaserod, with a modest effect in functional constipation, has been withdrawn due to concern over adverse effects. Lubiprostone, with its novel mechanism of action on stool consistency, has received FDA approval. A number of agents are under investigation for this common complaint: probiotics and prebiotics (carbohydrates stimulating the activity of beneficial colonic bacterial flora), subcutaneous neurotrophin-3 (a nerve growth factor), oral opiate antagonists, and mixed 5-HT<sub>4</sub> receptor agonist / 5-HT<sub>3</sub> receptor antagonists.

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## IS THERE A ROLE FOR PHARMABIOTICS?

■ *Eamonn Quigley*

While a rationale for the use of probiotics can be developed for a number of functional gastrointestinal symptoms and syndromes, and an experimental basis for their use continues to emerge, the data base of well-conducted clinical trials of probiotics in this area remains slim. Irritable bowel syndrome (IBS) has attracted the most attention, recent revelations with regard to the potential roles of the enteric flora and immune activation in the pathogenesis of IBS leading to a re-awakening of interest in bacteriotherapy in this common and challenging disorder. Some recent randomized controlled studies attest to the efficacy of some probiotics in alleviating individual IBS symptoms while selected strains have a more global impact. Evidence for long-term efficacy is also beginning to emerge though more studies are needed in this regard. In other functional syndromes, data is far from adequate to make recommendations despite evidence for efficacy of probiotics in treating individual symptoms such as diarrhea, constipation and bloating. Several other issues complicate the interpretation of much of the literature in this area: lack of quality control; use of many different species and strains; and, above all, significant deficiencies in trial methodology. Prebiotics, substances that promote the growth of commensal species, have actually been used for some time in the treatment of constipation, whether as fibre, bulking agents or Lactulose; in this context the relative contributions of the prebiotic properties of these compounds has not been differentiated from their other effects on colonic motility or fluid exchange.

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## THE ROLE OF THE COLORECTAL NURSE SPECIALIST

 **Theresa Porrett**

Despite constipation being the most common gastrointestinal complaint leading to a medical consultation, not all institutions, and consequently not all patients, have access to dedicated biofeedback departments. Although efficacy of biofeedback has been demonstrated, specific focus on the form of treatment has perhaps impacted negatively on a range of other nurse-led therapies. A majority of constipated individuals will respond to lifestyle alteration, dietary modification and bowel and toilet habit retraining. Given the often overbooked and busy proctological clinic environment, in which secondary symptoms of constipation (haemorrhoids) rather than the underlying cause is treated, the education and management of this group of patients legitimately falls within the remit of an experienced and suitably trained Colorectal Nurse Specialist (CRNS). Equally those patients whose constipation symptoms arise from rectal evacuatory dysfunction (such as rectocoele and intussusception) can be symptomatically improved by nurse-led bowel retraining and education alongside techniques such as bowel irrigation.

This paper will explore the role of the CRNS in the management and support of patients with simple constipation and in those with evacuatory dysfunction. The key components of behavioural therapy will be addressed including: lifestyle alteration; education and support regarding compliance with laxative regimes; challenging behaviour with respect to the inappropriate response to the call to stool; teaching effective defaecating posture; establishing a defaecating routine; and the avoidance of straining. Anal irrigation will be described and its use in constipation discussed.

The format and regularity of nurse-led regimes will be reviewed (group therapy sessions and individualised consultations) alongside the training and resources required to provide nurse-led behavioural therapies.

The CRNS is an effective adjunct to the conservative management of patients with constipation and can offer a range of supportive, educational and management regimes which can improve both the symptomatology and anxiety and depression of patients with constipation.

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## BEHAVIOURAL THERAPY, AND A CRITICAL APPRAISAL OF BOWEL RETRAINING

■ **Bill Whitehead**

One of the commonest causes of constipation in both children and adults is dyssynergic defecation (DD), which is defined by inadequate emptying of the rectum due to paradoxical contraction or failure to relax pelvic floor muscles during attempted defecation. This is a behavioural disorder; it occurs in the absence of neurological and anatomical abnormalities and is believed to represent maladaptive learning. Biofeedback and habit training are the principal treatments.

Biofeedback training requires five or six 45 minute sessions. Success depends partly on the experience of the therapist (often a nurse, physical therapist, or psychologist) and patient motivation. Training involves the following steps:

1. education about pelvic floor physiology and how the patient's responses lead to outlet obstruction;
2. straining training – insuring that the patient knows how to increase intra-abdominal pressure by contracting abdominal wall muscles;
3. relaxation of pelvic floor during straining – use of electronic feedback on anal canal pressure or pelvic floor EMG to teach the patient how to relax pelvic floor muscles during straining efforts;
4. practice simulated defaecation;
5. sensory training. Teaching the patient to recognize weaker sensations of rectal fullness by graded distensions of a rectal balloon.

Randomized controlled trials in adults with DD show that biofeedback is superior to laxatives <sup>1</sup>, sham biofeedback <sup>2</sup>, and a muscle relaxing drug <sup>3</sup>. Thus, biofeedback is the preferred treatment for DD in adults. However, in children biofeedback is no better than laxatives combined with bowel retraining <sup>4</sup>. Differences in outcome between children and adults are believed to be due to the requirement for sustained attention and high motivation for biofeedback.

Bowel retraining (also called habit training) was developed for and has been evaluated primarily in children. The elements are as follows:

1. patient / parent education about the physiology of defecation and the diagnostic findings for the patient;
2. disimpaction. Begin by clearing any faecal impaction with laxatives, enemas, or suppositories;
3. habit training. Patients are encouraged to attempt defecation at a consistent time each day, which should be 15 – 30 minutes after a meal;
4. fibre supplements or laxatives are usually prescribed.
5. depending on the child's age, parents may provide rewards for bowel movements.

Controlled studies evaluating the efficacy of bowel retraining are few <sup>5</sup>. A recent randomized control trial failed to show that bowel retraining added significantly to laxative treatment. Further studies are needed.

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## EVOLVING AND FUTURE MEDICAL THERAPIES

■ *Jan Tack*

Chronic constipation is a common condition for which dietary and lifestyle measures are usually the first-line therapy. When these fail, a variety of prescription and consumer laxatives are used. However, some patients do not respond well to or are not satisfied with chronic laxative use. A number of new drugs are currently being investigated for the treatment of (refractory) constipation. These include 5-HT<sub>4</sub> agonists, agents that act on intestinal secretion, and peripherally acting mu-opioid receptor antagonists. While Tegaserod, the first 5-HT<sub>4</sub> receptor agonist used in the treatment of chronic constipation, is now withdrawn from the market, a number of other 5-HT<sub>4</sub> receptor agonists such as Prucalopride, Renzapride and TD-5108. Three 12 week, double-blind, placebo-controlled, randomised studies in patients with chronic constipation confirmed the efficacy and safety of Prucalopride at the recommended dose of 2 mg daily. Lubiprostone and Linaclotide are novel agents which are effective in the treatment of constipation through luminal stimulation of intestinal secretion. Lubiprostone is a chloride channel activator which was shown to be efficacious in phase 3 studies in chronic constipation, and which is already available in the USA. Linaclotide is a small peptide that acts in the intestine to secrete chloride secretion through activation of the luminal receptor guanylate cyclase-C on enterocytes. Phase 2 studies confirmed efficacy in chronic constipation. Opioid antagonists such as Alvimopan or Methylnaltrexone are mainly used in opioid-induced constipation and postoperative ileus. Mechanistic studies suggest a potential for treatment of non-opiate chronic constipation too.

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## SURGERY FOR SEVERE RECTAL EVACUATORY PROBLEMS: DOES ANYTHING WORK?

■ **Mario Pescatori**

Surgery alone is unlikely to achieve good outcome in constipated patients with obstructed defecation in the long-term, and should be reserved to a minority of cases not responding to proper conservative treatment. The iceberg diagram may help to better evaluate the frequent occult lesions, both functional and organic, associated with rectocoele and mucosal prolapse (the tips of the iceberg), and therefore help to choose the appropriate treatment. The correction of the anatomical lesion does not necessarily mean correction of the corresponding functional abnormality.

Either open and laparoscopic sacral and resection rectopexy, and rectocoele repair carry high recurrent rates in the long term. STARR has an appealing rationale but is ineffective in patients with large rectocoele and may be followed by severe chronic proctalgia, recto-vaginal fistulae and life-threatening pelvic sepsis. A combined abdominal and transanal-transperineal procedure with prosthetic mesh may be preferable in patients with rectocoele associated with enterocoele and rectal intussusception. The low-invasive antegrade enema maybe helpful in selected cases.

A multidisciplinary approach is mandatory, as psychological, gastroenterological, neuromuscular and urogynaecological dysfunctions often affect patients with severe rectal evacuatory problems. Tailored surgery, which carries a low complication and re-intervention rate at our Unit, should be performed in selected cases by specialized colorectal and pelvic floor surgeons, able to treat associated functional disorders.

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## IS THERE A STILL A ROLE FOR COLECTOMY?

■ **Charles Knowles**

Patients with constipation usually come to the attention of the surgeon when conservative measures have failed to alleviate sufficiently severe symptoms. Following detailed clinical and physiologic assessment, the surgeon should attempt to tailor the procedure to specific underlying physiologic abnormalities in an attempt to restore function. Using this rationale, subtotal colectomy, and less so segmental resections, have been advocated to address colonic contractile dysfunction, manifest as slow-transit constipation, by resection of the perceived offending organ. It is now well recognised that the initial enthusiasm for this procedure should be tempered by recognition of the variable success rates, functional outcome measures and complication rates associated with such irreversible interventions<sup>1,2</sup>. Nevertheless, using rigorous patient selection, good results remain achievable using this approach. This session will critically review the outcome data for colonic resections in constipation. It will then focus on current position controversies including clinical and physiological selection criteria, role of segmental resection, minimally invasive approaches and the place of colectomy in comparison with other available contemporary treatments.

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## SACRAL NERVE NEUROMODULATION: THE NEW FRONTIER IN TREATMENT?

■ *Harald Rosen*

For almost 20 years, sacral nerve stimulation (SNS) has been a standardized treatment for urological disorders such as detrusor dysfunction and urinary retention, and more recently for faecal incontinence. In some patients treated for one or more of these indications, a positive influence on coexisting constipation has been observed. After the first clinical application using temporary SNS to treat slow colonic transit and / or rectal outlet obstruction, positive results in some patients have led to permanent implant procedures. However, until now, available data are restricted to experiences in a limited number of patients who had been implanted, ranging from 2 – 45 patients. Mid-term follow-up shows somewhat controversial results with rates of symptom improvement between 0 – 84%. Although questions regarding the mechanism of action of SNS on bowel motility and rectal physiology, as well clinical problems (patient evaluation, duration of the test phase, etc.) need to be further elucidated, the minimally invasive nature of the SNS test makes it an interesting new tool for the treatment for some patients suffering from chronic constipation.

### Notes

## Notes





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