

NEUROGASTROENTEROLOGIA

PROCEEDINGS

International Symposium *ANEMGI ONLUS* on

**APPROACH TO THE PATIENT WITH
DISORDERS OF INTESTINAL FUNCTION
FUNCTIONAL INTESTINAL DISORDERS**

ROMA, FEBRUARY 8-11, 2006 - Hotel CAVALIERI HILTON - Via Cadlolo, 101



Associazione per la NeUroGastroenterologia
e la Motilità Gastrointestinale
(ANEMGI ONLUS)

ANEMGI
V.le M. Pilsudski, 118 - 00197 Roma
Tel. / Fax +39 068078303 - e-mail: anemgi@anemgi.org - www.anemgi.org

ANEMGI is a non-profit organization devoted to promote research, education and care of visceral dysfunctions in patients with nervous system alterations.

ANEMGI ONLUS

President

Enrico S. Corazziari

Public relations

Emanuela Crescini



NeUroGastroenterologia

Is the official publication of the Associazione per la NeUroGastroenterologia e la Motilità Gastrointestinale (ANEMGI)

NeUroGastroenterologia attempts to bridge the gap between research and patient care by transferring scientific advances from different competences and disciplines to those entrusted with the management of patients with visceral disorders and alterations of the nervous system.

Aim of the Journal *NeUroGastroenterologia* is to publish topics which are relevant for specialists, family practitioners and other health personnel involved in this multidisciplinary area.

Material to be published includes: editorial, review article, original article, case report.

MESSAGGI
Edizioni

Publisher

MESSAGGI s.r.l.

Via G. Sismondi, 44 - 20133 Milano

Tel. +39 0276110205 Fax +39 027381635 - e-mail: messaggi_srl@tin.it - www.messaggi-publisher.org

Editor

Enrico S. Corazziari

ANEMGI WELCOME

It gives me a special pleasure to welcome you in Rome to participate to this International Symposium on "APPROACH TO THE PATIENT WITH DISORDERS OF INTESTINAL FUNCTION", promoted by the ANEMGI-Onlus (Associazione per la NeUroGastroenterologia e la Motilità Gastrointestinale).

The borderline between organic and non organic bowel disorders is not clear cut and has moved in the last 50 years to encompass many newly identified organic conditions such as lactase deficiency, small bowel bacterial overgrowth, bile acid malabsorption, subclinical manifestations of coeliac and inflammatory bowel disease, and drug-induced enterocolitis. In addition a relevant number of patients apparently belonging to the non-organic group because of normal endoscopic and laboratory findings at a more in depth investigations presents minimal change inflammatory lesions that are not yet well categorized and straddle on the organic non-organic borderline. Other patients belong to both sides of the organic non-organic borderline as they present both conditions or they have non-organic disorders following the resolution of organic ones such as postinfective IBS or functional bowel disorders during the remission periods of ulcerative colitis.

Not even the dichotomic concept of the psychologically induced functional disorders versus the organic disease holds true since the demonstration that the psychological stress can alter the permeability, and the immune response, of the gastroenteric mucosa.

In addition, at our current state of knowledge the available investigations are not always able to detect structural or biochemical alterations or to discriminate them from genuine disorders of function.

In conclusion, the widely accepted and used term of functional GI disorder (FGID), that will be maintained in the present text, is a misnomer that does not consider sufficiently the evolving knowledge of the pathophysiology of these conditions. Furthermore the term "functional" characterizes FGID for what they are not, i.e. the absence of organic causes and does not have any specific aetiological or pathogenetic connotations. The use of the terms "idiopathic disorder of gastrointestinal function" for describing these conditions is proposed to avoid the ambiguous term functional and to overcome the contraposition of organic versus non-organic versus psychological aetiology.

The diagnostic criteria known as Rome criteria have classified the Functional Bowel Disorders (FBD) into mutually exclusive categories based on predefined consensus criteria. This classification is useful to identify clinically homogeneous populations, however, in many patients, these predefined consensus criteria do not match natural clustering of symptoms, time course of symptom presentation, and physician's judgement of patient's symptoms.

In addition predefined consensus criteria have progressively (from Manning to Rome I and Rome II Criteria), excluded patients not matching the major clinical presentations of FBD (quasi syndromes) and have led to emarginate patients presenting two or more clinical categories (overlap syndromes).

The ANEMGI has promoted this symposium to provide critical and updated information useful for the management of patients with the different clinical presentations of FBD. These include both the major syndromes (IBS, IBS subtypes, Functional Constipation, Functional Diarrhoea, Pelvic Floor Dyssynergia, Abdominal Bloating) and the quasi syndromes (unspecified syndromes) or the overlap syndromes.

The uncertainty to discriminate the different etiological factors of bowel disorders and abdominal pain/bloating illness in FBD is reflected in the clinical practice where physicians are faced with a challenging differential diagnosis.

It is in fact more and more difficult e.g. to separate pure functional from minimal microscopic lesions, to categorize postinfectious bowel disorder, or to deal with syndromes in which functional and organic alterations coexist or alternate.

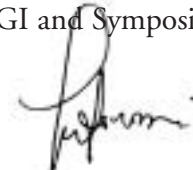
Also peculiar of FBD is the overlap with functional dyspepsia or gastro-oesophageal reflux disease and the practical need to deal with complex management of patients presenting with both lower and upper gastrointestinal disturbances.

The Symposium is focused to discuss the separate categories of FBD, quasi FBD and Overlap Syndromes under three main headings according to a patient-centered clinical presentation: common features, diarrhoeal illness and constipation illness.

It is wish of the ANEMGI that the Symposium will provide critical and updated information useful for the management of patients with the different clinical presentations of FBD and promote stimulating discussion and debate.

I should like to close by thanking you for your participation and hoping you will have a pleasant stay in Rome.

Enrico Corazziari
ANEMGI and Symposium President



International Symposium *ANEMGI ONLUS* on

APPROACH TO THE PATIENT WITH DISORDERS OF INTESTINAL FUNCTION FUNCTIONAL INTESTINAL DISORDERS

ROMA, FEBRUARY 8-11, 2006 - Hotel CAVALIERI HILTON - Via Cadlolo, 101

This Meeting was made possible thanks to the contribution provided by:

**NOVARTIS
PHARMA**

**SOLVAY
PHARMACEUTICALS**

**ALFA
WASSERMANN**

and

**BOEHRINGER
INGELHEIM**

- ❖ ACQUA E TERME DI ULIVETO
- ❖ AGPHARMA
- ❖ ASTRAZENECA
- ❖ BRACCO
- ❖ CA.DI.GROUP
- ❖ CHIESI
- ❖ DSMEDICA
- ❖ GIULIANI
- ❖ GSK USA
- ❖ ITALCHIMICI
- ❖ MENFIS
- ❖ NATHURA
- ❖ NOOS
- ❖ NORGINE
- ❖ PROMEFARM
- ❖ SCHERING PLOUGH
- ❖ SIFFRA
- ❖ SIGMA-TAU
- ❖ SMART PILL

ROTTAPHARM

SOFAR

APPROACH TO THE PATIENT WITH DISORDERS OF INTESTINAL FUNCTION

FUNCTIONAL INTESTINAL DISORDERS

ROMA, FEBRUARY 8-11, 2006

Hotel CAVALIERI HILTON Via Cadlolo, 101



John Ratner, "Medicine Man", 1989

ORGANIZING SECRETARIAT

MESSAGGI srl

Via Sismondi 44 - 20133 Milan (Italy)

Tel +39 0276110205 - Fax +39 027381635 - messaggi_srl@tin.it

International Symposium *ANEMGI ONIUS* on

**APPROACH TO THE PATIENT WITH
DISORDERS OF INTESTINAL FUNCTION**
FUNCTIONAL INTESTINAL DISORDERS

ROMA, FEBRUARY 8-11, 2006 - Hotel CAVALIERI HILTON - Via Cadlolo, 101

PRESIDENT

Enrico Corazziari

INTERNATIONAL SCIENTIFIC COMMITTEE

E Corazziari (Italy), *M Delvaux* (France), *DA Drossman* (USA),
G Holtmann (Germany), *J-R Malagelada* (Spain), *EA Mayer* (USA),
S Mueller-Lissner (Germany), *JF Tack* (Belgium),
W Grant Thompson (Canada), *WE Whitehead* (USA),
PJ Whorwell (UK)

FACULTY

DF Altomare, A Attili, S Auricchio, F Azpiroz, D Badiali, G Barbara,
G Basilisco, L Bueno, M Campieri, M Cicala, SM Collins, GR Corazza,
E Corazziari, M Corsetti, S Cucchiara, R Cuomo, R De Giorgio,
GF Delle Fave, MM Delvaux, F De Ponti, C Di Lorenzo, L Drago,
DA Drossman, MJG Farthing, G Gasbarrini, W Grant Thompson,
FI Habib, GJ Holtmann, EJ Irvine, MA Kamm, GR Locke III,
J-R Malagelada, EA Mayer, F Mearin, S Mueller-Lissner, F Pace,
F Pallone, N Pallotta, EMM Quigley, N Read, E Roda, C Scarpignato,
RC Spiller, A Staiano, V Stanghellini, J Tack, M Tonini, I Vantini,
P Vernia, WE Whitehead, PJ Whorwell

SCIENTIFIC SECRETARY

Danilo Badiali

Tel. +39 064469965 - secretariat@roma2006.org

COORDINATOR

Emanuela Crescini

Tel +39 0276110205 - Fax +39 027381635 - messaggi_srl@tin.it

Programme

Programme and Proceedings

February 8, 2006

- Arrival
- REGISTRATION 17.00 - 19.30
- Welcome Cocktail 19.30 - 21.30

Day 1

❖ February 9, 2006	REGISTRATION	7.30 - 8.30
	WELCOME	8.30

⇒ COMMON FEATURES OF DISORDERS OF INTESTINAL FUNCTION

Session 1 COMMON FEATURES OF DISORDERS OF INTESTINAL FUNCTION

Chairman **EMM Quigley**, *Cork, Ireland*

- 8.35 Definition and common features **E Corazziari**, *Rome, Italy*
- 9.00 Categorization of disorders of intestinal function **GJ Holtmann**, *Adelaide, Australia*
- 9.25 Epidemiology, individual and socio-economic burden **GR Locke**, *Rochester, USA*
- 9.50 Gender, genetics, and family environment **WE Whitehead**, *Chapel Hill, USA*
- 10.15 Assessment and treatment of psychological aspects **N Read**, *Ilkley, UK*
- 10.40 Altered sensitivity and motor function: any test? **M Delvaux**, *Nancy, France*

11.05 *Coffee break*

Poster viewing

Session 2 CLINICAL PRESENTATION

Chairman **A Attili**, *Rome, Italy*

Moderator **G Barbara**, *Bologna, Italy*

- 11.30 Alternating bowel **F Mearin**, *Barcelona, Spain*
- 11.55 Abdominal pain related and unrelated with bowel alterations **EA Mayer**, *Los Angeles, USA*
- 12.20 Pathophysiology of abdominal bloating **F Azpiroz**, *Barcelona, Spain*
- 12.45 Clinical presentation of abdominal bloating **J-R Malagelada**, *Barcelona, Spain*

13.10 *Lunch*

WORKSHOP on PROBIOTICS

Chairman **P Vernia**, *Rome, Italy*

- 14.30 Definition, Classification and quality control of microbiological activity **L Drago**
- 14.55 Mechanism of action **M Campieri**
- 15.20 Experience in childhood **S Cucchiara**

15.50 *Coffee break*

Poster viewing

Session 3 TREATMENT OF ABDOMINAL PAIN AND DISCOMFORT

Chairman **G Gasbarrini**, *Rome, Italy*

Moderator **R De Giorgio**, *Bologna, Italy*

- 16.20 Therapeutic approach to abdominal pain **DA Drossman**, *Chapel Hill, USA*
- 16.45 Treatment of abdominal pain and discomfort by manipulation of intestinal flora with probiotics and prebiotics **EMM Quigley**, *Cork, Ireland*
- 17.10 Treatment of functional symptoms by manipulation of intestinal flora with antibiotics **GR Corazza**, *Pavia, Italy*
- 17.35 Management of abdominal pain in children **C Di Lorenzo**, *Columbus, USA*

Day 2

❖ February 10, 2006

⇒ DIARRHOEAL ILLNESS AND ANAL CONTINENCE CONTROL IN DISORDERS OF INTESTINAL FUNCTION

Session 1 PATOPHYSIOLOGY AND CLINICAL PRESENTATION OF DIARRHOEAL ILLNESS

Chairman **F Pallone**, *Rome, Italy*

Moderator **R Cuomo**, *Naples, Italy*

- 8.00 Symptomatic manifestations of diarrhoeal illness **RC Spiller**, *Nottingham, UK*
8.25 Mechanisms of diarrhoea in disorders of intestinal function
PJ Whorwell, *Manchester, UK*
8.50 Postinfectious disorders of intestinal function **SM Collins**, *Hamilton, Canada*
9.15 Disorders of intestinal function in patients with organic bowel disease
EJ Irvine, *Toronto, Canada*
9.40 Mechanisms of anorectal physiology in diarrhoeal illness **G Basilisco**, *Milan, Italy*
10.05 Clinical presentation of diarrhoea in disorders of bowel function
MJG Farthing, *London, UK*
10.30 *Coffee break*
Poster viewing
and
discussion with the Authors

Session 2 OVERLAPPING SYNDROMES IN DIARRHOEAL ILLNESS

Chairman **V Stanghellini**, *Bologna, Italy*

Moderator **J Tack**, *Leuven, Belgium*

- 11.30 Diarrhoeal illness in patients with gastro-oesophageal reflux disease
F Pace, *Milan, Italy*
11.55 Diarrhoeal illness in patients with functional dyspepsia
M Corsetti, *Milan, Italy*
12.20 FREE PAPER SESSION
13.20 *Lunch*

Session 3 TREATMENT OF DIARRHOEAL ILLNESS

Chairman **MJG Farthing**, *London, UK*

Moderator **M Cicala**, *Rome, Italy*

- 14.30 Treatment of diarrhoea by manipulation of intestinal flora
M Campieri *Bologna, Italy*
14.55 Pharmacological treatment of diarrhoea **J Tack**, *Leuven, Belgium*
15.20 Management of diarrhoea in children **S Auricchio**, *Naples, Italy*
15.45 *Coffee*
16.00 SATELLITE SYMPOSIUM

Social Event at Hotel Cavalieri Hilton

18.00 *Musical performance* by *A Corazziari and M Grienti*
Music by *M Musorgskj G Crumb*

19.15 *Wine & Cheese*

Day 3

❖ February 11, 2006

⇒ CONSTIPATION ILLNESS IN DISORDERS OF INTESTINAL FUNCTION

Session 1 PATHOPHYSIOLOGY AND CLINICAL PRESENTATION OF CONSTIPATION ILLNESS

Chairman **E Roda**, *Bologna, Italy*

Moderator **S Mueller-Lissner**, *Berlin, Germany*

- 08.00 Mechanisms of constipation **MA Kamm**, *London, UK*
08.25 Pelvic and rectal alterations in constipation illness **FI Habib**, *Rome, Italy*
08.50 Clinical presentation of constipation illness **D Badiali**, *Rome, Italy*
09.15 Constipation illness in patients with upper gastrointestinal disorders
N Pallotta, *Rome, Italy*

09.40 **FREE PAPER SESSION**

10.40 *Coffee break*

Poster viewing

Session 2 TREATMENT OF CONSTIPATION ILLNESS

Chairman **GF Delle Fave**, *Rome, Italy*

Moderator **I Vantini**, *Verona, Italy*

- 11.05 Pharmacological treatment of constipation illness **S Mueller-Lissner**, *Berlin, Germany*
11.30 Non pharmacological treatment of constipation **DF Altomare**, *Bari, Italy*
11.55 Management of constipation illness in children **A Staiano**, *Naples, Italy*
12.20 **DIAGNOSTIC-THERAPEUTIC ALGORITHMS IN PATIENTS WITH DISORDERS
OF INTESTINAL FUNCTION** **E Corazziari**, *Rome, Italy*

13.00 *Lunch*

Session 3 EMERGING THERAPIES

Chairman **M Tonini**, *Pavia, Italy*

Moderator **E Corazziari**, *Rome, Italy*

- 14.00 Opening remarks **E Corazziari**, *Rome, Italy* **M Tonini**, *Pavia, Italy*
14.10 The significance of the placebo response in treating disorders of intestinal function
W Grant Thompson, *Ottawa, Canada*
14.35 Serotonergic drugs for the treatment of disorders of intestinal function **M Tonini**, *Pavia, Italy*
15.00 Tachykinin receptor blockade and gastrointestinal function: which antagonism
should be preferred to treat disorders of intestinal function? **F De Ponti**, *Bologna, Italy*
15.25 Role of CCK1 receptors in the control of gastrointestinal motor function and visceral pain
L Bueno, *Toulouse, France*
15.50 Opioid system and gastrointestinal function: new perspectives for drug development
C Scarpignato, *Parma, Italy*
16.15 Conclusion of the Symposium **E Corazziari**, *Rome, Italy*

16.30 *Coffee*

Lectures

- *Index*
- *Summaries*

	<i>Page</i>
<p>1 • DEFINITION AND COMMON FEATURES OF FUNCTIONAL GASTROINTESTINAL DISORDERS E CORAZZIARI <i>Gastroenterology A. Department of Clinical Sciences, University “La Sapienza”, Policlinico Umberto I, Rome, Italy</i></p>	19
<p>2 • CATEGORIZATION OF FUNCTIONAL GASTROINTESTINAL DISORDERS G HOLTSMANN <i>Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital and University of Adelaide, Adelaide, South Australia</i></p>	20
<p>3 • EPIDEMIOLOGY, INDIVIDUAL AND SOCIO-ECONOMIC BURDEN GR LOCKE III <i>Mayo Clinic College of Medicine, Rochester, USA</i></p>	22
<p>4 • GENDER, GENETICS, AND FAMILY ENVIRONMENT WE WHITEHEAD <i>Center for Functional GI & Motility Disorders University of NC at Chapel Hill Chapel Hill, North Carolina, USA</i></p>	22
<p>5 • ASSESSMENT AND TREATMENT OF PSYCHOLOGICAL ASPECTS OF FUNCTIONAL INTESTINAL DISORDERS N READ <i>Gastroenterologist, Psychotherapist and Writer Medical Adviser. IBS Network Ikley, West Yorkshire, UK</i></p>	24
<p>6 • ALTERED SENSITIVITY AND MOTOR FUNCTION IN FUNCTIONAL INTESTINAL DISORDERS: ANY TEST? MM DELVAUX <i>Department of Internal Medicine and Digestive Pathology, Hôpitaux de Brabois Adultes CHU de Nancy, Vandoeuvre les Nancy, France</i></p>	25
<p>7 • ALTERNATING BOWEL DISORDERS IN FUNCTIONAL GASTROINTESTINAL DISORDERS F MEARIN <i>Institute of Functional and Motor Digestive Disorders, Centro Médico Teknon, Barcelona, Spain</i></p>	25
<p>8 • ABDOMINAL PAIN, RELATED AND UNRELATED TO BOWEL HABIT ALTERATIONS, IN FUNCTIONAL INTESTINAL DISORDERS EA MAYER <i>Center for Neurovisceral Sciences & Women’s Health, Los Angeles, California, USA</i></p>	26
<p>9 • PATHOPHYSIOLOGY OF ABDOMINAL BLOATING F AZPIROZ <i>Digestive System Research Unit, University Hospital Vall d’Hebron, Barcelona, Spain</i></p>	27

Index

	<i>Page</i>
<p>10 • CLINICAL PRESENTATION OF ABDOMINAL BLOATING J-R MALAGELADA <i>Hospital General Vall'Hebron, Barcelona, Spain</i></p>	28
<p>11 • THERAPEUTIC APPROACH TO ABDOMINAL PAIN IN FUNCTIONAL GASTROINTESTINAL DISORDERS DA DROSSMAN <i>UNC Center for Functional GI and Motility Disorders Division of Gastroenterology and Hepatology UNC School of Medicine, Chapel Hill, North Caroline, USA</i></p>	29
<p>12 • TREATMENT OF ABDOMINAL PAIN AND DISCOMFORT BY MANIPULATION OF THE INTESTINAL FLORA WITH PROBIOTICS AND PREBIOTICS EMM QUIGLEY <i>Alimentary Pharmabiotic Centre, University College, Cork, Ireland</i></p>	30
<p>13 • TREATMENT OF FUNCTIONAL SYMPTOMS BY MANIPULATION OF INTESTINAL FLORA WITH ANTIBIOTICS IN DISORDERS OF INTESTINAL FUNCTION GR CORAZZA, M DI STEFANO <i>I Department of Internal Medicine, University of Pavia, IRCCS "S.Matteo" Hospital, Pavia, Italy</i></p>	31
<p>14 • MANAGEMENT OF FUNCTIONAL ABDOMINAL PAIN IN CHILDREN C DI LORENZO <i>Children's Hospital of Columbus The Ohio State University, Columbus, OHIO, USA</i></p>	32
<p>15 • SYMPTOMATIC MANIFESTATIONS OF DIARRHOEAL ILLNESS RC SPILLER <i>Wolfson Digestive Diseases Centre, University Hospital, Nottingham, UK</i></p>	34
<p>16 • MECHANISMS OF DIARRHOEA IN FUNCTIONAL GASTROINTESTINAL DISORDERS PJ WHORWELL <i>Department of Medicine, University Hospital of South Manchester Nell Lane, West Didsbury, Manchester, UK</i></p>	35
<p>17 • POST-INFECTIVE GUT DYSFUNCTION: DIARRHOEA S COLLINS <i>McMaster University, Hamilton, Ontario Canada</i></p>	36
<p>18 • DIARRHOEAL ILLNESS EJ IRVINE <i>University of Toronto, Head, Division of Gastroenterology St. Michael's Hospital, Toronto, Canada</i></p>	36

	<i>Page</i>
19 • MECHANISMS OF ANORECTAL PHYSIOLOGY IN DIARRHOEAL ILLNESS G BASILISCO <i>Gastroenterology Unit, IRCCS Ospedale Maggiore Policlinico, Milan, Italy</i>	37
20 • CLINICAL PRESENTATION OF DIARRHOEA IN FUNCTIONAL BOWEL DISORDERS MJG FARTHING <i>St George's, University of London, London, UK</i>	38
21 • DIARRHOEAL ILLNESS IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX DISEASE F PACE, S PALLOTTA <i>Department of Gastroenterology, University Hospital "Luigi Sacco", Milan, Italy</i>	40
22 • DIARRHOEA DISORDERS IN SUBJECTS WITH FUNCTIONAL DYSPEPSIA M CORSETTI <i>Gastroenterology Unit, University Vita-Salute, IRCCS Hospital "San Raffaele", Milan, Italy</i>	40
23 • TREATMENT OF DIARRHOEA BY MANIPULATION OF INTESTINAL FLORA M CAMPIERI, KM LAMMERS, P GIONCHETTI, C MORSELLI, F RIZZELLO, R TAMBASCO, G BAZZOCCHI <i>University of Bologna, Bologna, Italy</i>	42
24 • PHARMACOLOGICAL TREATMENT OF DIARRHOEA IN PATIENTS WITH FUNCTIONAL INTESTINAL DISORDERS J TACK <i>Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium</i>	44
25 • MANAGEMENT OF DIARRHOEA IN CHILDREN WITH DISORDERS OF INTESTINAL FUNCTION E MIELE, S AURICCHIO <i>Department of Pediatrics, University of Naples "Federico II", Naples, Italy</i>	45
26 • MECHANISMS OF CONSTIPATION IN FUNCTIONAL DISORDERS MA KAMM <i>Physiology Unit, St Mark's Hospital, London, UK</i>	46
27 • PELVIC AND RECTAL ALTERATIONS IN CONSTIPATION ILLNESS FI HABIB <i>Department of Clinical Sciences University "La Sapienza", Rome, Italy</i>	47
28 • CLINICAL PRESENTATION OF CONSTIPATION ILLNESS D BADIALI <i>Department of Clinical Sciences University "La Sapienza", Rome, Italy</i>	48

Index

	<i>Page</i>
29 • CONSTIPATION IN PATIENTS WITH UPPER GASTROINTESTINAL DISORDERS N PALLOTTA <i>Department of Clinical Sciences University “La Sapienza”, Rome, Italy</i>	49
30 • PHARMACOLOGICAL TREATMENT OF CONSTIPATION S MUELLER-LISSNER <i>Humboldt University, Department of Internal Medicine, Park-Klinik Weissensee, Berlin, Germany</i>	51
31 • NON-PHARMACOLOGICAL TREATMENT OF CONSTIPATION DF ALTOMARE <i>Department of Emergency and Organ Transplantation, General Surgery and Liver Transplantation Unit, University of Bari, Italy</i>	52
32 • MANAGEMENT OF CONSTIPATION IN CHILDREN WITH DISORDERS OF INTESTINAL FUNCTION A STAIANO <i>Department of Pediatrics, University “FedericoII”, Naples Italy</i>	54
33 • THE SIGNIFICANCE OF THE PLACEBO RESPONSE IN FUNCTIONAL GASTROINTESTINAL DISORDERS W GRANT THOMPSON <i>University of Ottawa, Ottawa, Canada</i>	55
34 • SEROTONERGIC DRUGS FOR THE TREATMENT OF DISORDERS OF INTESTINAL FUNCTION M TONINI <i>Department of Physiological and Pharmacological Sciences, University of Pavia, Pavia, Italy</i>	56
35 • TACHYKININ RECEPTOR BLOCKADE AND GASTROINTESTINAL FUNCTION: WHICH ANTAGONISM SHOULD BE PREFERRED TO TREAT DISORDERS OF INTESTINAL FUNCTION? F DE PONTI <i>Department of Pharmacology, University of Bologna, Bologna, Italy</i>	57
36 • ROLE OF CCK1 RECEPTORS IN THE CONTROL OF GASTROINTESTINAL MOTOR FUNCTION AND VISCERAL PAIN L BUENO <i>Neurogastroenterology Unit INRA, Toulouse, France</i>	59
37 • OPIOID SYSTEM AND GASTROINTESTINAL FUNCTION: NEW PERSPECTIVES FOR DRUG DEVELOPMENT C SCARPIGNATO <i>Laboratory of Clinical Pharmacology, School of Medicine & Dentistry University of Parma, Parma, Italy</i>	60

DEFINITION AND COMMON FEATURES OF FUNCTIONAL GASTROINTESTINAL DISORDERS

E CORAZZIARI

Gastroenterology A. Department of Clinical Sciences, University "La Sapienza", Policlinico Umberto I, Rome, Italy

Definition

"Functional gastrointestinal disorder" (FGID) defines various combinations of chronic or recurrent gastrointestinal (GI) symptoms that cannot be explained on the basis of structural or biochemical abnormalities. It is interesting that the definition characterises FGIDs for what they are not, and that it is not even based on the presence of a physiological abnormality: in some cases, no physiological abnormalities have been identified; in others, their presence may not accompany symptoms or may coincide with the symptom-free intervals of intermittent symptoms, and it is unclear what the cause-and-effect relationship between the two may be. Furthermore, the word "functional" has no specific etiological or pathogenetic connotations, and can even be considered misleading as it is generally used to denote the absence of organic disease or conditions defined after the exclusion of organic disease, whereas the definition of FGID does not necessarily preclude the presence of structural or biochemical abnormalities but only those causing the symptoms. In addition, FGIDs and organic diseases may coexist, such as IBS in the presence of colonic diverticula or gallstones, or an FGID may follow or persist after the resolution of an organic disease: e.g. patients may present IBS symptoms in the absence of any inflammatory lesions after an episode of infectious gastroenteritis, or during the remission phases of ulcerative colitis. Finally, the available investigations are not always capable of detecting structural or biochemical alterations, or of discriminating them from pure disorders of function. In conclusion, although largely accepted and widely used, FGID is a misnomer that does not give sufficient consideration to the many characteristics of these disorders and the new and still increasing knowledge of their pathophysiology. It would in fact be more appropriate to use the term "idiopathic disorders of gastrointestinal function", as this would avoid the use of the word "functional" and overcome the contraposition of organic and non-organic etiologies.

Common features

The Rome criteria¹ have defined and classified 24 FGIDs into six sub-categories based on five anatomical regions: esophageal, gastroduodenal, bowel, biliary and anorectal plus functional abdominal pain. However, patients with clinically different symptoms have a number of common characteristics.

The preponderance of females in most FGID categories² indicates a common relevant role for either biological factors that are due to sex or environmental and/or behavioural factors due to gender. FGID sufferers show similar health-seeking behaviour, although it tends to be limited to a small proportion of the vast number of affected subjects in the community. Irrespective of category, they are characterised by more psychiatric diagnoses and psychosocial disturbances³⁻⁷, are more susceptible to stress,⁸ and show a high degree of abnormal illness behaviour⁹. Many also present a wide range of extra-gastrointestinal symptoms, thus suggesting the con-

comitant involvement of several organs due to a generalised derangement of the autonomic nervous system¹⁰⁻¹¹.

A large number of FGID patients in all symptom categories¹² show a visceral hypersensitivity¹³⁻¹⁴ that can be interpreted as a derangement in the way the central nervous system modulates afferent visceral signals¹⁵.

Many subjects have two or more FGIDs, or complain of symptoms related to more than one. Functional dyspepsia is often associated with functional bowel disorders, and IBS has been reported in 23-50% of dyspeptic patients¹⁶⁻²⁰.

Categorization cannot properly take into consideration the frequent overlapping of symptoms between different FGIDs: e.g. it is not known how to delineate the borderline that separates subjects with functional constipation from those with constipation-predominant IBS and those with pelvic floor dyssynergia. A classification that favours the use of homogenous and predefined categories inevitably leads to the exclusion of well-known clinical features that do not cluster into repeatable patterns to the same extent, such as rectal urgency or post-prandial abdominal pain and, as a consequence, a number of subjects cannot be classified on the basis of specific symptomatic patterns but are placed into unspecified subgroups. This is not a trivial issue because, for example, the Rome I criteria classifies as many as 23% of dyspeptic patients as belonging to the group with unspecified dyspepsia²¹.

In conclusion, drawing distinctions between categories may involve different etiological conditions and could disregard the frequent similarities of disorders that may actually share a common pathophysiological mechanism.

REFERENCES

1. Drossman DA, Corazziari E, Talley NJ, et al. Rome II Functional Gastrointestinal Disorders. Degenon Ass, McLean VA: 2000.
2. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. *Dig Dis Sci* 1993;38:1569-1580.
3. Young SJ, Alpers DH, Norland CC, et al. Psychiatric illness and the irritable bowel syndrome: practical implications for the primary physician. *Gastroenterology* 1976;70:162-66.
4. Palmer RL, Crisp AH, Sonehill E, et al. Psychological characteristics of patients with the irritable bowel syndrome. *Postgr Med J* 1974;50:416-19.
5. Magni G, Di Mario F, Bernasconi G, et al. DSM-III diagnoses associated with dyspepsia of unknown cause. *Am J Psych* 1987;144:1222-23.
6. Walker EA, Roy-Byrne PP, Katon WJ, et al. Psychiatric illness and irritable bowel syndrome: a comparison with inflammatory bowel disease. *Am J Psych* 1990;147:1656-61.
7. Craig TKJ, Brown GW. Goal frustration and life events in the aetiology of painful gastrointestinal disorder. *J Psychos Res* 1984;28:411-21.
8. Whitehead WE, Crowell MD, Robinson JC, et al. Effects of stressful life events on bowel symptoms: subjects with irritable bowel syndrome compared to subjects without bowel dysfunction. *Gut* 1992;33:825-30.
9. Whitehead WE, Winget C, Fedoravicius AS, et al. Learned illness

Lectures

- behaviour in patients with irritable bowel syndrome and peptic ulcer. *Dig Dis Sci* 1982;27:202-208.
10. Yunus MB, Masti AT, Aldgag JC. A controlled study of primary fibromyalgia syndrome: clinical features and association with other functional syndromes. *J Rheumatol* 1989;16:62-71.
 11. Whorwell PJ, Lupton EW, Erduran D, Wilson K. Bladder smooth muscle dysfunction in patients with Irritable Bowel Syndrome. *Gut* 1986;27:1014-1017.
 12. Holtmann G, Goebell H, Talley NJ. Functional dyspepsia and irritable bowel syndrome: is there a common pathophysiological basis? *Am J Gastroenterol* 1997;92:954-9.
 13. Richter JE, Barish CF, Castell DO. Abnormal sensory perception in patients with esophageal chest pain. *Gastroenterology* 1986;91:845-52.
 14. Mearin F, Cucula M, Azpiroz F, et al. The origin of symptoms on the brain-gut axis in functional dyspepsia. *Gastroenterology* 1991;101:999-1006.
 15. Mayer EA, Raybould HE. Role of visceral afferent mechanisms in functional bowel disorders. *Gastroenterology* 1990;99:1688-1704.
 16. Talley NJ, Weaver AL, Tesmer DL. Lack of discriminant value of dyspepsia subgroups in patients referred for upper endoscopy. *Gastroenterology* 1993;105:1378-86.
 17. Crean GP, Holden RJ, Knill-Jones RP, et al. A database on dyspepsia. *Gut* 1994;35:191-202.
 18. Talley NJ, Piper DW. The association between non-ulcer dyspepsia and other gastrointestinal disorders. *Scand J Gastroenterol* 1985;20:896-900.
 19. Talley NJ, Weaver AL, Zinmeister AR, Melton LJ III. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992;136:165-77.
 20. Agreus L, Svardsudd K, Nyren O, et al. Irritable bowel syndrome and dyspepsia in the population: overlap and lack of stability over time. *Gastroenterology* 1995;109:671-80.
 21. Talley NJ, Zinmeister AR, Schleck CD, Melton LJ III. Dyspepsia and dyspepsia subgroups: a population based study. *Gastroenterology* 1992;102:1259-1268.

CATEGORIZATION OF FUNCTIONAL GASTROINTESTINAL DISORDERS

GJ HOLTSMANN

Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital and University of Adelaide, Adelaide, South Australia

Introduction

Categorization of diseases is usually based upon structural or biochemical abnormalities. Diagnosing specific disorders - which basically represents categorization of diseases - intends to group conditions with common underlying abnormalities. Thus categorization facilitates treatment by grouping disorders with common pathophysiologies. In addition, categorization of diseases may allow predicting the prognosis of a given patient with regard to response to therapy or the long term outcome. Similarly, categorization of so called functional gastrointestinal disorders (disorders of intestinal function) is supposed to serve the same purpose. By definition there is a lack of structural or biochemical abnormalities in patients with functional gastrointestinal disorders that can be identified utilising clinically available routine testing¹. Thus the classic approach of categorization based upon structural or biochemical abnormalities is not feasible in patients with functional gastrointestinal disorders.

Categorization based upon symptoms

In the absence of structural lesions, attempts have been made to categorise functional disorders based upon the symptoms. Characteristics of symptoms (e.g., fullness, pain, nausea, bloating) as well as the localisation of symptoms (upper or lower gut), were used to categorize patients into more or less heterogenous categories (e.g., functional dyspepsia, irritable bowel syndrome). These categories were mainly consensus based while only a limited number of studies has properly attempted to apply valid methodologies². Unfortunately symptom categories overlap³. In a series of 157 consecutive patients with functional GI disorders 43% simultaneously reported upper and lower gut symptoms while 43% had dyspepsia alone. In addition there is lack of stability over time. Indeed, a large proportion of patients fluctuate between functional dyspepsia, IBS, or a combination of both⁴.

Categorization based upon abnormalities of function

It is now widely believed that abnormalities of motor or sensory function are present in a proportion of patients with functional GI disorders⁵. It thus appears logical to categorize patients based upon underlying abnormalities. Unfortunately there is as yet insufficient evidence that this approach is justified. In general function testing has been done in patients referred to tertiary centres. Only a limited number of studies have assessed abnormalities of function in non health care seeking subjects. However, one study demonstrated delayed gastric emptying and an augmented symptom response to a standardised nutrient challenge in population based (non-healthcare seeking) subjects with dyspepsia⁶. On the other hand, the role of disordered motor and sensory function for the symptom manifestation remains to be determined. Abnormalities of function may simply represent markers of underlying

pathophysiologies hence the association between abnormal function and symptoms is only present in subgroups of patients ⁷.

Categorization based upon initiating events

It is now believed that a proportion of patients manifest symptoms after an acute gastrointestinal infection. So far there are limited data suggesting that an initiating infectious event is important for the response to therapy or the long term prognosis.

Molecular markers

Considering the disturbances of gastrointestinal function, polymorphisms of adrenergic, opioidergic or serotonergic receptors as well as G-protein β_3 (GNB3) subunit gene polymorphisms (C825T) and polymorphisms of 5-HT transporter genes and other molecular markers are suitable for categorization of functional GI disorders. Thus, relevant polymorphisms of genes with immune-modulating and/or neuro-modulating features (OPRM1, IL-4, IL-4R, TNF α) may also play a role in the manifestation of functional GI disorders. Based upon this a two step model for the role of genetic factors for the manifestation of functional pain is proposed. While research in the field of the molecular markers or risk factors may contribute to our understanding of the underlying pathophysiologies, it is as yet not proven that these molecular markers are of value for the categorization of patients with functional GI disorders.

Summary and conclusions

There are different approaches for the categorization of functional gastrointestinal disorders. The ideal categorization should guide treatment and should allow predicting the long-term outcome of patients. Unfortunately, there is currently no perfect categorization that serves these purposes. In the routine clinical setting, the assessment of the most dominant symptom might be sufficient and appropriate. In the context of clinical trials, a more complex categorization of symptoms might be more useful. Symptoms should be assessed utilising validated instruments that take into account not only the presence but also the severity of symptoms. In addition, abnormalities of function should be recorded whenever possible. Furthermore, potential underlying molecular mechanisms should be noted. Thus the ultimate categorization should include a dimension of the symptom pattern (e.g. pain-dominant functional dyspepsia), a dimension of function testing (e.g. normal gastric emptying test and augmented symptom response during a nutrient challenge) and in the future potentially relevant molecular markers such as the GNB3 status or polymorphisms of 5-HT transporter genes.

REFERENCES

1. Drossman DA. Rome II: a multinational consensus document on functional gastrointestinal disorders. In: Corazziari E, ed. 2002:1-81.
2. Talley NJ, Holtmann G, Agreus L, Jones M. Gastrointestinal symptoms and subjects cluster into distinct upper and lower groupings in the community: a four nations study. *Am J Gastroenterol* 2000; 95:1439-1447.
3. Holtmann G, Goebell H, Talley NJ. Functional dyspepsia and irritable bowel syndrome: Is there a common pathophysiological basis? *Am J Gastroenterol* 1997;92:954-959.
4. Agreus L, Svärdsudd K, Nyren O, Tibblin G. Irritable bowel syndrome and dyspepsia in the general population: overlap and lack of stability over time. *Gastroenterology* 1995;109:671-680.
5. Talley NJ. Review article: Functional dyspepsia - Should treatment be targeted on disturbed physiology? *Aliment Pharmacol Ther* 1995;9:107-115.
6. Haag S, Talley NJ, Holtmann G. Symptom patterns in functional dyspepsia and irritable bowel syndrome: relationship to disturbances in gastric emptying and response to a nutrient challenge in consulters and non-consulters. *Gut* 2004;53:1445-1451.
7. Stanghellini V, Tosetti C, Paternico A, et al. Risk indicators of delayed gastric emptying of solids in patients with functional dyspepsia. *Gastroenterology* 1996;110:1036-1042.

Lectures

EPIDEMIOLOGY, INDIVIDUAL AND SOCIO-ECONOMIC BURDEN

GR LOCKE III

Mayo Clinic College of Medicine, Rochester, USA

The disorders of gastrointestinal function are all quite common. Among these disorders, irritable bowel syndrome (IBS), functional diarrhoea and functional faecal incontinence are each associated with diarrhoea and anal continence control problems¹. Symptoms of IBS are reported by 10 to 20% of the population^{2,3}, chronic recurrent diarrhoea by up to 26% and episodes of faecal incontinence by up to 18%. These community surveys measure symptom reporting however these people usually have not had an investigation; and thus the actual number of people with these symptoms who do not have an alternative explanation for their symptoms is not known. Still, when these people are investigated, most of them do not have anatomic, biochemical or endoscopic abnormalities and thus meet the criteria for IBS, functional diarrhoea or functional faecal incontinence. These symptoms tend to come and go which makes determination of the incidence of these conditions quite difficult⁴. These disorders have an impact on quality of life and are associated with significant health care costs. Few studies have combined these conditions to assess the impact of diarrhoeal illness and anal continence control in disorders of gastrointestinal function, but individually, IBS, functional diarrhoea and functional anal incontinence certainly place a heavy burden on individuals and society^{5,6}.

REFERENCES

1. Drossman DA, Corazziari E, Talley NJ, et al. Rome II - The functional gastrointestinal disorders. In: Drossman DA, editors. McLean, VA: Degnon Associates; 2000; 764.
2. Drossman DA, Li Z, Andruzzi E, et al. U.S. householder survey of functional gastrointestinal disorders. Prevalence, sociodemography, and health impact. *Dig Dis Sci* 1993;38:1569-80.
3. Agreus L, Svardsudd K, Nyren O, et al. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population. A report from the Abdominal Symptom Study. *Scand J Gastroenterol* 1994;29:102-9.
4. Locke GR, III, Yawn BP, Wollan PC, et al. Incidence of a clinical diagnosis of the irritable bowel syndrome in a United States population. *Aliment Pharmacol Ther* 2004;19:1025-31.
5. Hahn BA, Yan S, Strassels S. Impact of irritable bowel syndrome on quality of life and resource use in the United States and United Kingdom. *Digestion* 1999;60:77-81.
6. Locke GR, 3rd, Zinsmeister AR, Fett SL, et al. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol & Motil* 2005;17:29-34.

GENDER, GENETICS, AND FAMILY ENVIRONMENT

WE WHITEHEAD

Center for Functional GI & Motility Disorders

University of NC at Chapel Hill

Chapel Hill, North Carolina, USA

Symptom differences between men and women

Most community based epidemiological studies which used symptom-based diagnostic criteria have reported the prevalence of irritable bowel syndrome (IBS) to be greater in women than in men by a ratio of approximately 2:1¹. In Asian countries, however, IBS appears to be only slightly more prevalent in women than in men². Some Asian studies have reported a greater prevalence in men, but sample bias is suspected to account for these inconsistencies.

In the United States and other Western countries, when samples are obtained from clinics or when clinical diagnosis rather than diagnosis based on symptom criteria is employed, women outnumber men by a larger ratio of approximately 4:1. This occurs because, in Western countries, women are more likely than men to seek medical care after adjusting for differences in type and severity of disease. This gender difference in medical consultation may be reversed in Japan and other Asian countries.

Women are also more likely than men to report the symptom of constipation, and radio- opaque marker studies show that, on average, women have slower whole gut transit. Data on gender differences in constipation in Asian countries are not available for comparison.

Women are also more likely than men to report abdominal pain and to consult doctors for treatment of abdominal pain. Laboratory studies confirm a lower somatic pain threshold in women relative to men, but for visceral pain, reports have been inconsistent.

Reproductive hormones and gastrointestinal symptoms

Several community-based surveys have shown that the prevalence of IBS (diagnosed by Rome symptom criteria) decreases following menopause in women but not in men. In addition to a lower prevalence, the severity of IBS symptoms in women who continue to meet criteria for IBS diagnosis, decreases following menopause. These observations suggest that estrogen and other female reproductive hormones play a role in the etiology or course of IBS. However, other observations suggest that this role must be indirect: (1) IBS symptoms show little variation between the luteal and follicular phases of the menstrual cycle but are highest during menstrual flow when levels of estrogen and progesterone are lowest. Moreover, Whorwell's group reports that visceral pain thresholds in women with IBS are lowest during menstrual flow. (2) Most women with IBS who become pregnant report that their symptom severity decreases during pregnancy, although estrogen levels remain high during pregnancy. These data suggest that IBS symptom severity is related to menstruation and that estrogen and progesterone play an indirect role by setting the stage for menstruation to occur.

Genetics

IBS and possibly other functional GI disorders cluster within

families. The children of young adults with IBS (both fathers and mothers) are more likely to be brought to the pediatrician for abdominal pain, diarrhoea, or other GI symptoms compared to the children of parents without IBS³. Moreover, twin studies show a concordance for IBS diagnosis in monozygotic twins that is approximately twice the concordance seen in dizygotic twins⁴. These twin studies are consistent with a genetic contribution to IBS etiology and course, but with several caveats: (1) The overall concordance rate is rather low, suggesting that having a monozygotic twin with IBS increases the risk of developing IBS by about 10-20%. (2) In most twin studies, the twins were raised together, making it difficult to separate genetic from environmental causes for concordance. (3) The concordance rate between parent and child is as great as the concordance rate for monozygotic twins, and it is greater than the concordance rate for dizygotic twins. This suggests that there are shared environmental influences that are as great as the influence of shared genes.

It has been suggested that a twin studies may be an insensitive way to assess genetic influences on IBS because IBS may be a heterogeneous disorder: genetic polymorphisms may be more closely associated to some subtypes of IBS than to others. The first genotyping study in IBS patients appeared very promising despite a small sample size (n=30): Camilleri et al reported that polymorphisms in the SERT gene (long/long forms of the gene), which regulates the reuptake of serotonin from the synaptic cleft, was associated with differences in whether the 5HT₃ antagonist, alosetron, was able to slow transit (the long/long polymorphism was associated with greater responsiveness to alosetron than the heterozygous form). The investigators speculated that the drug's effect on transit was likely to be predictive of its effects on symptoms of IBS-D.

Pata et al also examined the association of SERT polymorphisms in IBS vs controls and found no differences. However, when they divided their sample into constipation-predominant IBS (IBS-C), diarrhoea-predominant IBS (IBS-D), and alternators (IBS-A), they found a higher prevalence of the short/short polymorphism in IBS-C and of the heterozygote pattern (s/l) in the IBS-D subgroups. In a follow-up to their original study Kim, Camilleri et al⁵ examined the association between SERT, alpha-2 adrenergic, and norepinephrine polymorphisms in IBS patients. They failed to replicate an association between SERT polymorphisms and any IBS subtype but did observe a significant association between IBS-C and two polymorphisms in the alpha-2 adrenoceptor. Yeo et al screened a variety of 5HT polymorphisms in women with IBS-D and healthy controls, and they found an association between a deletion/deletion polymorphism in the promoter region for SERT, which is a different SERT polymorphism than was previously reported by Camilleri to be associated with IBS-D. Thus, the data published to date provide no consistent evidence that genetic polymorphisms are significantly associated with IBS as a whole or with any subtype of IBS. Further study is needed.

Family environment

The clustering of IBS within families may be due to family influences that are independent of genetics. Levy, Whitehead et al have suggested that social learning in the form of imitation by children of the ways their parents behave when ill and parental encouragement of somatic complaints, may contribute to the intergenera-

tional transmission of illness behaviours. They have also emphasized that the intergenerational transmission of illness behaviour is not limited to GI symptoms: mothers with IBS have a variety of comorbid conditions including psychological symptoms, and their children likewise report an excess number of non-GI as well as GI symptoms.

REFERENCES

1. Mayer EA, Naliboff B, Lee O, Munakata J, Chang L. Review article: gender-related differences in functional gastrointestinal disorders. *Aliment Pharmacol Ther* 1999;13:65-69.
2. Gwee KA. Irritable bowel syndrome in developing countries--a disorder of civilization or colonization? *Neurogastroenterol Motil* 2005;17:317-324.
3. Levy RL, Whitehead WE, Walker LS, et al. Increased somatic complaints and health-care utilization in children: effects of parent IBS status and parent response to gastrointestinal symptoms. *Am J Gastroenterol* 2004;99:2442-2451.
4. Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 2001;121:799-804.
5. Kim HJ, Camilleri M, Carlson PJ, et al. Association of distinct alpha(2) adrenoceptor and serotonin transporter polymorphisms with constipation and somatic symptoms in functional gastrointestinal disorders. *Gut* 2004;53:829-837.

Lectures

ASSESSMENT AND TREATMENT OF PSYCHOLOGICAL ASPECTS OF FUNCTIONAL INTESTINAL DISORDERS

N READ

Gastroenterologist, Psychotherapist and Writer
Medical Adviser, IBS Network
Ikley, West Yorkshire, UK

Anger, fear and desperation are so frequently expressed as disturbances in gastrointestinal function that to all intents and purposes, the gut may be considered part of the limbic system. We are all familiar with the diarrhoea that may accompany apprehension, the constipation that may be associated with melancholy and the way frustration can seem to give us abdominal pain, but often these disturbances disappear as soon as whatever causes them is resolved. If we can put these gut reactions into context and so generate and resolve an emotion then they can be eliminated. If, however, whatever has happened is so upsetting that it cannot be thought about or if the situation cannot be resolved, then the feelings can persist and are consolidated as a chronic disorder of gastro-intestinal function, such as Irritable Bowel Syndrome, Functional Dyspepsia and Chronic Abdominal Pain. Such conditions are often resistant to medical treatment, but psychological treatments can be very effective.

When assessing the patient with chronic, 'medically-unexplained' disturbances in gastrointestinal function, it is more important to understand the patient than the physiology. In other words, we must try to understand the conditions under which the disturbance of function developed.

Perhaps the most important question to explore is 'What was happening at the time the illness started'. Patients will often look surprised and say, 'Nothing!', but my experience is that detailed enquiry into the events around the time of the onset or exacerbation of the illness will nearly always identify an important change or upsetting occurrence. Don't be put off if the patient says something like, 'Oh, mum died last year, but I was expecting it and just got on with things.' Life changes or life events that are suppressed and ignored most frequently give rise to unexplained visceral symptoms. Other lines of enquiry that may help patients see their symptoms as expressions of what has happened to them include investigating when the symptoms go away and when they return. Does the illness get worse or get better when they go on holiday or at Christmas or when they go to work or when they are at home at weekends? There is often a reason for the waxing and waning of unexplained gastrointestinal disturbances and it is always important to investigate that. If this process is successful, patients will begin to experience a dawning realization of just how their symptoms may vary according to situations and events in their life. At this stage it is important to allow space for them to volunteer their own associations. Discoveries patients make for themselves are of more therapeutic benefit than suggestions made by the therapist. Once the patient is engaged in the process of contextualization, it is important for the therapist to consider what it is about a patient's life script that makes them react to certain situations defensively with illness. What does the situation mean for them? This often involves a detailed enquiry into the patient's childhood, marriage and work relationships. Once patients can understand why

they have become ill, then the therapist can enable them talk about and work through their difficulties and help them discover more healthy solutions. This type of therapy can not only give rise to resolution of the illness but also lead to a growth in understanding so that the symptoms are less likely to return so frequently or last so long. It doesn't always occur, however.

Not all patients can see or are willing to see the connection between life situations and bouts of illness. And even if they can understand the reason for their illness, the context may be so upsetting that further exploration is unhelpful and such they may retreat into an exacerbation of the illness. It is at this point that some patients may leave therapy. Sometimes the reason why one patient may react to life changes by becoming ill may be buried so deeply in the amnesia of infancy that they cannot be recalled. The assessment of patients for psychological treatments of disturbances of gastrointestinal function must therefore include an evaluation whether the patient is able to see the connection between life events and able to explore the reasons for them. Only those patients who can do this, are going to be suitable for exploratory, analytical or dynamic forms of psychotherapy.

For the many patients, who cannot access the reason why life events make them ill but can nevertheless appreciate the links between their symptoms and life events, less intrusive therapies such as cognitive behavioural therapy, are more suitable. Cognitive behavioural therapy helps the patient regard their symptoms, not as a mystery illness that the doctor can cure, but as the reactions to situations that cause emotional tension. The therapist will then help the patients deal with those situations in a more healthy way by suggesting strategies they may use to deal with their frustration, calm their fears and cope with feelings of desperation and hopelessness. For patients who are so anxious and depressed that they cannot think clearly, a course of antidepressants may give them the mental space to think and engage with therapy.

But there are still some patients who refuse to see any connections with life situations. For them, further psychological enquiry may just tend to reinforce their resistance and it is important instead to employ therapies as tools to give them a sense of confidence and control over their illness. Relaxation, meditation and hypnotherapy all reduce emotional tension and alleviate symptoms and generate confidence and control. They also have the added advantage that patients can also learn to apply these methods themselves. Biofeedback therapy directly trains patients how to manipulate their own bodily function. Complementary therapies provide that focus of belief and expectation that is such a powerful aspect of healing. For illnesses that are generated at the level of the idea, healing must be applied at the same level.

But in all types of therapy, the quality of the relationship with the therapist is of paramount importance. If patients are able to establish the sort of communication with their therapist that generates trust, then they are more likely to use the quality of the relationship to help them learn to keep themselves well.

REFERENCES

1. Blanchard EB, Scharff L. Psychosocial aspects of assessment and treatment of irritable bowel syndrome and recurrent abdominal pain

- in children. *J Consult Clin Psychol* 2002; 70: 725-738.
2. Creed F. on behalf of the North of England IBS Research Group. The cost effectiveness of psychotherapy and SSRI antidepressants for severe irritable bowel syndrome. *Gastroenterology* 2003;124:303-317.
 3. Drossman DA. Review article: an integrated approach to the irritable bowel syndrome. *Aliment Pharmacol Ther* 1999;13, Suppl 2:3-14.
 4. Read NW. Sick and Tired. Healing the illnesses doctors cannot cure. Ch.9. *Breaking the Mould*. London 2005; pp. 176-198.
 5. Watkins P. The efficacy of treatment: therapy or therapist. *J Royal Coll Phys* 2005;5:309-311.

ALTERED SENSITIVITY AND MOTOR FUNCTION IN FUNCTIONAL INTESTINAL DISORDERS: ANY TEST?

MM DELVAUX

Department of Internal Medicine and Digestive Pathology,
Hôpitaux de Brabois Adultes
CHU de Nancy, Vandoeuvre les Nancy, France

Diagnosis of functional digestive disorders remains until now mainly concentrated on symptom-based criteria that are mainly known as the Rome criteria and have been validated in several studies. These criteria allow a positive diagnosis of these disorders. However, a "biological marker" of the conditions is still lacking. Assessment of gut function in patients with functional GI disorders has mainly concentrated over years on motility disorders in the small and large intestines and more recently on abnormal visceral sensory responses as demonstrated by barostat distension studies. None of these tests has so far proven to be effective to discriminate fairly patients with functional disorders from those with organic conditions or healthy subjects. Abnormalities described as characteristic of patients with functional disorders are far from being constant and sometimes also found in healthy controls. In Irritable Bowel Syndrome (IBS), motility disorders are more linked to abnormal bowel habits than to pain episodes.

Functional tests have more largely been used in clinical research and they helped significantly to understand the pathophysiology of the disorders. Less evidence has so far been obtained that some of these tests could be used as predictors of the patient's response to pharmaceutical intervention. They have also failed to help identifying active drugs in human research.

ALTERNATING BOWEL DISORDERS IN FUNCTIONAL GASTROINTESTINAL DISORDERS

F MEARIN

Institute of Functional and Motor Digestive Disorders, Centro Médico Teknon, Barcelona, Spain

Disorders of the intestinal function, or functional bowel disorders, are defined as functional gastrointestinal disorders with symptoms attributable to the mid or lower gastrointestinal tract. Disorders of the intestinal function include the irritable bowel syndrome (IBS), functional abdominal bloating, functional constipation, functional diarrhoea, and unspecified functional bowel disorders. Thus, several clinical manifestations such as abdominal pain/discomfort, bloating, constipation and diarrhoea, are part of their symptomatic universe. In some cases patients have an abnormal but stable bowel habit, and constipation or diarrhoea is maintained over time. This is what happens in functional constipation, functional diarrhoea, constipation-predominant IBS (IBS-C) or diarrhoea-predominant IBS (IBS-D). However, in some other IBS patients disturbed defecation is not constant and alternates from diarrhoea to constipation, and viceversa. Such IBS patients with alternating bowel habit (IBS-A) are more difficult to treat because therapies targeted to improve a specific bowel habit abnormality (constipation or diarrhoea) might exacerbate it when switching from one bowel pattern to another.

IBS treatment is directed not only at alleviating abdominal discomfort/pain but also at normalising bowel habit. Thus, new therapies have been designed to specifically treat patients with diarrhoea or patients with constipation. Drugs such as alosetron and cilansetron, 5HT₃ antagonists, are clinically effective in alleviating pain and bowel-related symptoms in patients with IBS-D. By contrast, tegaserod, a 5HT₄ partial agonist, accelerates intestinal transit and improves symptoms in IBS-C. Therefore, it is important to determine bowel habit in individual IBS cases to be able to select the most appropriate therapy. The problem is that in many patients diarrhoea and constipation alternate, giving rise to the so-called IBS-A subtype. Whether IBS-A is part of IBS-C or IBS-D, depending on the predominant bowel alteration, or a different syndrome is not completely clear. Moreover, who or what should determine the IBS subtype (established clinical criteria, the physician or the patient himself) has not yet been clarified. Therefore, comparisons among studies are difficult. Moreover, the variability in the observed distribution of IBS in different studies can be attributed to other factors such as the existence of real differences of the syndrome in different populations, different overlap with other functional gastrointestinal disorders, and methodological differences in study design and questionnaire administration. Greater difficulties arise when studies on IBS subtypes are compared according to bowel habit.

In a systematic review recently published we have found differences on bowel habit predominance among most studies within each population source group. There are many reasons that explain disparities when comparing study results. First of all, real differences based on different populations located in different geographical areas may exist. Moreover, differences in applied diagnostic criteria, in participation rate and questionnaire compliance,

Lectures

as well as differences in methodology to evaluate symptoms, may contribute to explain different results. IBS definition and criteria to establish IBS subtypes according to bowel habit alterations affect IBS prevalence, subtype distribution, patient selection and gender distribution; therefore data obtained from different studies might not be comparable at all. On the other hand, information from different population source is not comparable. Characteristics of patients seeking medical care are different from those who do not. Available studies in the literature report IBS-D as the most frequent bowel pattern among people seeking health care and even as a predictor of referral to specialists. However, in our systematic review, we have found IBS-A to be the most frequently reported pattern among primary care office-based studies (consulters) and either IBS-C or IBS-D among gastroenterology specialized office-based studies.

It is to note that subjects with the alternating subtype seem to be more affected by abdominal pain/discomfort than those with other subtypes (constipation or diarrhoea). On the other hand, the level of nuisance caused by constipation and by diarrhoea is similar in subjects with IBS-A than in IBS-C and IBS-D, respectively. In fact, when analysing clinical manifestations in subjects meeting the criteria of IBS-A, we observed that this group was quite similar to the constipation subtype but with frequent defecatory urgency in the absence of an increased number of bowel movements.

If few attention has been paid to IBS-A much less to the bowel habit that predominates in these cases. Interestingly, we found that in 37 patients with IBS who considered themselves as having alternating bowel movements, 8 % reported bowel function consistent with a subtype classification of constipation, 11 % with diarrhoea and 62 % with no disturbed bowel habit.

REFERENCES

1. Thompson WG, Longstreth G, Drossman DA, Heaton K, Irvine EJ, Muller-Lissner S. Functional bowel disorders and functional abdominal pain. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. Rome II. The functional gastrointestinal disorders (2nd ed.). McLean, Virginia, Degnon Associates, 2000: 351-432.
2. Mearin F, Balboa A, Badía X, et al. Irritable bowel syndrome subtypes according to bowel habit: revisiting the alternating subtype. *Eur J Gastroenterol Hepatol* 2003;15:165-72.
3. Hungin AP, Whorwell PJ, Tack J, Mearin F. The prevalence, patterns and impact of irritable bowel syndrome: an international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003;17:643-50.
4. Mearin F, Baró E, Roset M, et al. Clinical patterns over time in Irritable Bowel Syndrome: symptom instability and severity variability. *Am J Gastroenterol* 2004;99:113-21.
5. Guilera M, Balboa A, Mearin F. Bowel habit subtypes and temporal patterns in irritable bowel syndrome. Systematic review. *Am J Gastroenterol* 2005;100:1174-84.

ABDOMINAL PAIN, RELATED AND UNRELATED TO BOWEL HABIT ALTERATIONS, IN FUNCTIONAL INTESTINAL DISORDERS

EA MAYER

Center for Neurovisceral Sciences & Women's Health, Los Angeles, California, USA

Abdominal pain and discomfort are the most common symptoms reported by patients with functional disorders of the GI tract. In the absence of detectable organic disease, these symptoms are thought to be related to an enhanced perception of visceral stimuli ("visceral hypersensitivity") with or without additional peripheral abnormalities¹. Depending on the association with alterations in bowel habits, these symptoms are either referred to as 1) irritable bowel syndrome (IBS) or as 2) functional abdominal pain (FAP).

1) According to the current Rome classification, pain has to be associated with altered bowel function in order to become a symptom criterion for the diagnosis of IBS². Regardless of predominant bowel habit, abdominal pain and discomfort are one of the hallmarks of IBS. Based on the failure to discriminate between pain and discomfort, it is generally unclear if pain or non-painful discomfort are the most bothersome symptom, if there is a difference in the pathophysiology between painful and nonpainful symptoms, or if the difference is simply one of individual semantics^{3,4}. In the majority of patients, pain is typically experienced over the left lower quadrant and is generally associated with a tender sigmoid colon both on palpation and on endoscopy. This pain is transient, crampy in nature and is typically relieved by passing a bowel movement. It is thought to be related to the enhanced perception of high amplitude sigmoid contractions preceding a bowel movement. The mechanism(s) underlying the enhanced perception remain to be determined, but are likely to include central pain amplification mechanisms¹. Non-painful discomfort associated with bowel movements occur in the form of urgency before, or as a sensation of incomplete evacuation following a bowel movement. Discomfort also occurs in the form of abdominal fullness and gas with or without distension. The pathophysiology of these different non-painful symptoms remains to be determined, but may also include alterations in normal pain modulation systems. 2) In FAP, abdominal pain and discomfort are typically more constant, with little relationship to food intake or bowel habits. The mechanism(s) underlying this type of pain are likely to differ from those mentioned for IBS⁵. Treatment responses of patients with abdominal pain and with IBS and in FAPs are different, further supporting the concept of different underlying neurobiological mechanisms.

REFERENCES

1. Schwetz I, Bradesi S, Mayer EA. Current insights into the pathophysiology of Irritable Bowel Syndrome. *Curr Gastroenterol Rep* 2003; 5:331-6.
2. Gastroenterology April 2006 - In press. Supplement on Rome III committee reports.
3. Lembo T, Naliboff B, Munakata J, et al. Symptoms and visceral per-

ception in patients with pain-predominant irritable bowel syndrome. *Am J Gastroenterol* 1999;94:1320-1326.

4. Sach J, Bolus R, FitzGerald L, Naliboff BD, Mayer EA. Is there a difference between IBS patients reporting abdominal pain or discomfort? *Am J Gastroenterol* 2002;97:3131-3138.
5. Clouse RE, Mayer EA, Aziz Q, et al. Functional Abdominal Pain Syndrome. In *Gastroenterology* 2006, April. Supplement on Rome III committee reports.

PATHOPHYSIOLOGY OF ABDOMINAL BLOATING

F AZPIROZ

Digestive System Research Unit, University Hospital Vall d'Hebron, Barcelona, Spain

Abdominal bloating is a common and significant clinical problem without proper clinical classification, known pathophysiology or effective treatment, that remains to be scientifically addressed¹. Bloating is one of the most common and bothersome complaints in a large proportion of patients with various functional gut disorders, but in the current standard classification abdominal bloating is merely regarded as a secondary descriptor. Four factors are included in the pathophysiology of bloating: subjective sensation of abdominal bloating, objective abdominal distension, volume of intraabdominal contents and muscular activity of the abdominal wall. The primer to elicit subjective bloating may be any of the other three factors, or else, the sensation may be related to distorted perception, and these mechanisms may play an independent role or may be interrelated. Bloating probably represents a heterogeneous condition produced by a combination of pathophysiological mechanisms, that differ among individual patients, and that in most cases are subtle and undetectable by conventional methods. Several studies measuring girth changes with either tape measure, computed tomography or inductance pletismography, have shown that, indeed, the subjective sensation is associated to objective abdominal distension². Gas production was initially measured by Levitt's group using a wash-out technique, and was found to be normal in patients³. Hydrogen, which accounts for a large proportion of colonic gas production, is partly absorbed into the blood and excreted by breath. A more recent study measured gas excretion (breath plus anal) by indirect calorimetry in IBS patients on a standard diet, and showed that hydrogen excreted was increased, but the total gas volume excreted (hydrogen plus methane) was not different than in healthy controls. Indirect evaluation of hydrogen production by breath tests has shown either normal production or increased production, attributed to various causes, such as hyperactive gas producing colonic flora, small bowel bacterial overgrowth or small bowel malabsorption. The level of evidence supporting these interpretations is questionable. Nevertheless, it seems that the total volume of gas produced in these patients is not much larger than in healthy subjects.

Three independent studies showed that the gas surface in plain ab-

dominal radiographs was somewhat larger in IBS patients than in controls, but the extra gas volume would hardly justify the symptoms. Furthermore, other studies using computed tomography or the wash-out technique, could not detect differences between patients complaining of bloating and healthy controls².

Gas transit studies have evidenced that patients with bloating have impaired handling of gut contents. Scintigraphic studies using gas labelled with radioactive xenon, indicate that the small bowel is responsible for impaired gas transit in these patients, in contrast to the common idea of gas being retained in the colon⁴. The ileocecal region is an area with sphincteric function likely implicated in this dysfunction. However, very elaborate studies with gas infusion at various levels of the gut showed that gas retention is due to impaired propulsion in more proximal parts of the small bowel, because while jejunal gas loads were retained, clearance of gas directly infused into the distal ileum or the cecum was normal. Impaired gas clearance in these patients is related to abnormal gut reflexes: the prokinetic effect of gut distension is impaired and the inhibitory effect of intestinal lipids are up-regulated, and both effects, reduced stimulation and increased inhibition, contribute to delayed gas transit and retention⁵. Hence, segmental pooling, either of gas or alternatively of solid/liquid components, may induce bloating sensation, particularly in patients with altered gut perception.

It has been recently shown that an intraabdominal volume load, produced by colonic gas infusion, induces in healthy subjects an increment in tonic activity of the abdominal muscles, that can be measured by electromyography, and this response is probably mediated via viscerosomatic reflexes. This adaptation of the abdominal wall to intraabdominal volume loads is impaired in patients complaining of bloating, who fail to contract their abdominal muscles, and this abnormal response is associated to exaggerated abdominal distension and bloating. Hence, altered viscerosomatic reflexes may contribute to abdominal wall protrusion and objective distension, even without net intraabdominal volume increments.

The combination of the interacting pathophysiological factors may determine the clinical presentation of bloating and related symptoms. A more precise knowledge of the pathophysiology and clinical forms of bloating may allow the development of mechanistic rather than the currently empiric treatment strategies, for a comprehensive and effective management of this heterogeneous problem.

REFERENCES

1. Azpiroz F, Malagelada J-R. Abdominal bloating. *Gastroenterology* 2005;129:1060-1078.
2. Maxton DG, Martin DF, Whorwell P, et al. Abdominal distension in female patients with irritable bowel syndrome: exploration of possible mechanisms. *Gut* 1991;32:662-4.
3. Levitt MD, Bond JH, Levitt DG. Gastrointestinal gas. In: Johnson LR, editor. *Physiology of the Gastrointestinal Tract*. New York: Raven, 1981:497-502.
4. Salvioli B, Serra J, Azpiroz F, et al. Origin of gas retention in patients with bloating. *Gastroenterology* 2005; 128:574-579.

Lectures

- Passos MC, Serra J, Azpiroz F, et al. Impaired reflex control of intestinal gas transit in patients with abdominal bloating. *Gut* 2005; 54:344-348.

CLINICAL PRESENTATION OF ABDOMINAL BLOATING

J-R MALAGELADA

Hospital General Vall'Hebron, Barcelona, Spain

Bloating is a feeling of distension in the abdomen that may or may not be accompanied by visible enlargement of the waist¹. There are many subcategories of bloating. First, there is epigastric bloating that may be part of the dyspepsia syndrome and that some patients describe without apparent distinction with epigastric pressure or even indigestion. This type of bloating centered in the upper abdomen may be present in chronic belchers who inflate their stomach by pumping air in. The bloated sensation in the upper abdomen may also occur in gastroparesis or subacute proximal small bowel obstruction, although under such circumstances nausea and /or vomiting are common accompanying features. Second, there is diffuse abdominal bloating which is the kind of bloating we refer to in clinical practice when we describe a bloated patient. It is also the category of bloating most patients refer to when complain of a sensation of distended abdomen and tight clothes. Diffuse abdominal bloating may be a feature of the irritable bowel syndrome (IBS) in which case it is associated with pain and altered bowel movement pattern or it may present as a sole or predominant symptom. In the latter case, the Rome II Consensus Committee on Functional Gut Disorders assigns it a separate category: functional bloating. Third, there may be bloating circumscribed to the lower abdomen and in that case the patient tends to acknowledge a more evident relation to inability to pass gas or stool.

A lot of people get bloated², but the levels of concern vary. Many healthy individuals may get bloated on occasion particularly after overindulging in a large meal or in association with an overload of fermentable foodstuffs. Such bloating tends to be relatively short-lasting – maximum a few hours – and terminates by passing stool and/or gas. Self-induced bloating is rarely a cause for concern or medical consultation because cultural background knowledge and experience has clearly taught the relation of bloating to a precipitant cause and subsequent prompt and spontaneous relief³. An important exception, however, are those individuals who are either so annoyed by postprandial bloating or with unrealistic expectations of overload tolerance that will consult not out of true concern about the significance of their symptom, but to obtain from the specialist some form of preventive therapy to allow them to eat what they please without feeling uncomfortable.

Bloating and flatulence are not synonymous, although they may coexist. Experimental evidence suggest that increasing fermentable substrate in the colon, for instance by administration of

a poorly absorbable disaccharide like lactulose will result in most healthy individuals in increase colonic gas production (mostly H₂) and flatulence⁴. However, under these circumstances bloating may not occur, since as we will see later, the normal gut is extremely efficient in disposing of increased gas loads by rapid evacuation. If the rate of production increases beyond the maximal rate of excretion, or in individuals (healthy or otherwise) who behave as “gas retainers” bloating will result. However, even then it will be self limited bloating that will resolve after gas evacuation rates catch up with production or retention. This analysis coincides with clinical observations that suggest that most people who consult because of increased flatulence do not complain of bloating. The reverse situation may occur. Bloating may be a prominent feature in the absence of increased flatulence and again this appears to be the case for many complainers of bloating. These individuals may express a feeling that if they could expel gas they would feel better and, in fact, this is how bloaters obtain (admittedly not very often) relief. Levitt has nicely demonstrated the disparities between bloating and flatulence by observing the responses to oral loads of either lactulose (fermentable) or Psyllium (non fermentable) in a group of healthy volunteers. In the first instance both flatulence and bloating scores tended to increased whereas in the second only bloating scores did⁵.

REFERENCES

- Alvarez W. Hysterical type of nongaseous abdominal bloating. *Arch Intern Med* 1949;84:217-245.
- Sandler RS, Stewart WF, Liberman JN, Ricci JA, Zorich NL. Abdominal pain, bloating, and diarrhea in the United States: prevalence and impact. *Dig Dis Sci* 2000;45:1166-1171.
- Maxton DG, Whorwell PJ. Abdominal distension in irritable bowel syndrome: the patient's perception. *Eur J Gastroenterol Hepatol* 1992;4:241-243.
- Furne JK, Levitt MD. Factors influencing frequency of flatus emission by healthy subjects. *Dig Dis Sci* 1996;41:1631-1635.
- Suarez FL, Levitt MD. Intestinal gas. In: Feldman M, Friedman LS, and Sleisenger MH, eds. *Gastrointestinal and liver diseases: pathophysiology/diagnosis/management*. Philadelphia, PA WB Sanders Co: 2002:155-163.

THERAPEUTIC APPROACH TO ABDOMINAL PAIN IN FUNCTIONAL GASTROINTESTINAL DISORDERS

DA DROSSMAN

UNC Center for Functional GI and Motility Disorders
 Division of Gastroenterology and Hepatology
 UNC School of Medicine, Chapel Hill, North Caroline, USA

Introduction

With the evolving of knowledge of the brain-gut axis, there is a greater understanding of the mechanisms and treatments for chronic abdominal pain. This presentation will cover the central (i.e., CNS) mechanisms for chronic pain and the approach to treatment.

Diagnoses

Within the Rome II classification system, the one condition that typifies chronic abdominal pain is Functional Abdominal Pain Syndrome and in some cases, the same treatments would apply to severe chronic irritable bowel ^{1,2}. For further details regarding the diagnostic criteria for these disorders, the reader is referred elsewhere ³.

Chronic Pain in Functional GI Disorders

For FGID's the underlying pathophysiology and the clinical determinants of the pain relates to any of 4 characteristics: increased motor reactivity, visceral hypersensitivity, altered mucosal immunity with inflammation, and dysregulation of central modulation of pain ⁴. As shown in Table 1, as the pain becomes more severe (i.e., constant, continuous and prolonged), patients having chronic pain are more often seen in tertiary care settings, and the symptoms tend to have less gut physiological correlation (i.e., worsened with eating and relieved with defecation). The pain becomes more constant with disruption in usual activities, greater health care use and maladaptive illness behaviours and more co-morbid psychiatric diagnoses. The physiological evidence suggests that this type of pain is more related to abnormalities in the CNS modulation of visceral signals than any increase in visceral activity. For this reason, the use of centrally active agents that improve CNS downregulation is indicated.

TABLE 1 - Continuum of severity with functional GI pain

	MILD	MODERATE	SEVERE
Estimated Prevalence	70%	20%	5%
Clinical Setting	Primary	Secondary	Tertiary
Gut Physiologic Correlation	+++	++	+
Symptom Constancy	0	+	+++
Activity Disruption	0	+	+++
Health Care Use	+	++	+++
Illness Behaviour	0	+	+++
Psychiatric Diagnoses	0	+	+++

Treatment Approach

The treatment approach is based on several general guidelines:

1. **Effective Physician-Patient Relationship.** Details of this ap-

proach can be found elsewhere ⁵. In general, it is important for the physician to communicate empathy, accepting that the pain is real, set realistic goals for improvement, since cure is not likely, and involve the patient in treatment decisions. Generally better outcomes are obtained when patients feel more in control of their health care management. The physician also needs to educate the patient on the physiological determinants of the pain, which includes some discussion of the brain-gut axis and the gate-control theory where areas in the CNS are not functioning as well to "turn down" pain signals, and this opens the door to centrally targeted agents. Finally, patients need to be seen on a regular basis, either by the gastroenterologist or primary care physician, even if there ancillary mental health care treatments are utilized.

2. **Peripherally Acting Treatments.** The use of peripherally active treatments to reduce increased motor reactivity (e.g. antispasmodics) or visceral hypersensitivity (e.g. peripheral 5HT agents like tegaserod or alosetron) and less commonly non-steroidal analgesics, are not usually effective but can be tried for milder symptoms of pain.
3. **Antidepressants.** The antidepressants play a key role in treatment of chronic pain syndromes, via their central effects on enhancing central pain regulation ⁶, and in higher dosages, treating psychiatric co-morbidities. In general, the tricyclic antidepressants (e.g., desipramine, nortriptyline, amitriptyline) show greater benefit due to their combined serotonergic and noradrenergic activity. However, they can produce side effects of dizziness, dry mouth and constipation that is difficult to tolerate. The SSRI's (e.g., fluoxetine, citalopram, paroxetine) do not have as much benefit for pain, but can help associated anxiety, thus reducing the pain-anxiety vicious cycle. Recently, the use of SNRI's (selective serotonin-neuropinephrine reuptake inhibitors) like duloxetine and venlafaxine is likely to be helpful because it possesses the serotonin-noradrenergic activity of tricyclics without their side effects.
4. **Psychological Treatments.** These are recommended adjuncts due to recent studies showing their benefit, their safety margin and long lasting benefit, even after treatments end. Examples include cognitive-behavioural therapy, stress-management and relaxation, hypnosis and interpersonal psychotherapy. The reader is referred elsewhere for discussion of these treatments ⁷.

REFERENCES

1. Longstreth GE, Drossman DA. Severe Irritable Bowel And Functional Abdominal Pain Syndromes: Managing The Patient And Health Care Costs. Clin Gastroenterol Hepatol 2005; 3:397-400.
2. Drossman DA. Functional abdominal pain syndrome. Clin Gastroenterol Hepatol 2004;2:353-65.
3. Thompson WG, Longstreth GE, Drossman DA, Heaton KW, Irvine EJ, Mueller-Lissner S. Functional Bowel Disorders and Functional Abdominal Pain. In: Drossman DA, Talley NJ, Thompson WG, Whitehead WE, Corazziari E, eds. Rome II: Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment. 2 ed. McLean, VA: Degnon Associates, Inc.; 2000: 351-432.
4. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA

Lectures

- Technical Review on Irritable Bowel Syndrome. *Gastroenterology* 2002;123:2108-31.
5. Drossman DA. The Physician-Patient Relationship. In: Corazziari E, ed. *Approach to the Patient with Chronic Gastrointestinal Disorders*. Milan: Messaggi; 1999: 133-39.
 6. Dille J, Jones MP, Drossman DA. Understanding the mind-body connection in the functional GI disorders: Anatomic and physiologic relationships between the central nervous system and digestive tract. In: Jones MP, Crowell MD, eds. *Contemporary Diagnosis and Management of Functional Digestive Disorders*. 1 ed. Newton: Handbooks in Health Care; 2005.
 7. Drossman DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. In: Drossman DA, Corazziari E, Talley NJ, Thompson WG, Whitehead WE, eds. *Rome II. The functional gastrointestinal disorders: Diagnosis, pathophysiology and treatment; A multinational consensus*. 2 ed. Degenon and Associates; 2000: 157-245.

TREATMENT OF ABDOMINAL PAIN AND DISCOMFORT BY MANIPULATION OF THE INTESTINAL FLORA WITH PROBIOTICS AND PREBIOTICS

EMM QUIGLEY

Alimentary Pharmabiotic Centre, University College, Cork, Ireland

With an ever-increasing appreciation of the role of the gut flora in homeostasis in health and disease, interest has also increased in the potential for strategies which can manipulate the gut flora to prove of therapeutic benefit in a range of intestinal and extra-intestinal disorders. The idea of using probiotics in the management of abdominal pain and discomfort, the cardinal symptoms of irritable bowel syndrome (IBS) may, at first sight, appear surprising. However, recent developments in our understanding of IBS have provided a rationale for this therapeutic approach. Probiotics have several actions that could be of benefit in IBS. These include antibacterial, immune modulating and mucosal barrier protective effects ¹. Probiotics can also induce quantitative and qualitative changes in the gut flora and alter stool mucus and bile salt composition. Qualitative changes in the flora could, in turn, reduce the abnormal colonic fermentation that has been reported, by some ², in IBS. Evidence now accumulates to suggest efficacy for certain probiotics, at least, in IBS. Nobaek et al evaluated the response of symptoms and the colonic flora to supplementation, for four weeks, with a rose-hip drink containing 5×10^7 cfu/ml of *Lactobacillus plantarum* (DSM 9843) and 0.009 g/ml oat flour ³. The latter may well have acted as a prebiotic. When evaluated one year later and when compared to a placebo-treated group, the probiotic group experienced a significant reduction in flatulence but not in abdominal pain or bloating. Kim et al investigated the effects of eight weeks of treatment with the probiotic cocktail, VSL#3, on gastrointestinal transit and symptoms in 25 patients with Rome II-positive IBS with predominant diarrhoea ⁴. While treatment with VSL#3 resulted in a reduction in abdominal bloating scores, there were no effects on other IBS symptoms such as abdominal pain, gas and urgency. In a further trial, the same group found that VSL# 3 reduced flatulence scores and retarded colonic transit but without altering bowel function among a group of patients with IBS and bloating ⁵. In the most promising study to date, O'Mahony et al compared the responses of symptoms and peripheral blood mononuclear cell cytokine ratios in IBS patients to ingestion of milk-based probiotic preparations containing either a lactobacillus or a bifidobacterium with a placebo in an eight-week study ⁶. Patients who were randomized to *B. infantis* 35624 reported a greater reduction in symptom scores; composite and individual scores for abdominal pain/discomfort, bloating/distention, and bowel movement difficulty were significantly lower than for placebo for those randomized to *B. infantis* 35624 for most weeks of the treatment phase. No consistent benefits were associated with therapy with the lactobacillus. Clues to the possible mode of action of the bifidobacterium were provided by the cytokine assays. At baseline, patients with IBS demonstrated an abnormal IL-10/IL-12 ratio, indicative of a proinflammatory, Th-1, state; this was normalised in the bifidobacterium

group alone. If these results are replicated in larger studies and if probiotics can be delivered in an encapsulated, consistent and quality-controlled manner, these “food supplements” may well move from the complementary alternative medicine (CAM) category into that of main stream pharmaceuticals. Further studies of the mode(s) of action of probiotics in IBS are also awaited with interest.

REFERENCES

1. Quigley EM. Use of probiotics in functional bowel disease. *Gastroenterol Clin North Am* 2005;34:533-45.
2. King TS, Elia M, Hunter JO. Abnormal colonic fermentation in the irritable bowel syndrome. *Lancet* 1998;352:1187-9.
3. Nobaek S, Johanson ML, Molin G, Ahrne S, Jeppsson B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* 2000;95:1231-8.
4. Kim HJ, Camilleri M, McKenzie S, Lempke MB, Burton DD. A randomized controlled trial of a probiotic, VSL#3 on gut transit and symptoms in diarrhoea-predominant IBS. *Aliment Pharmacol Ther* 2003;17:895-904.
5. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomised controlled trial of probiotic combination VSL#3 and placebo in IBS with bloating. *Neurogastroenterol Motil* 2005;17:687-96.
6. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology* 2005;128:541-51.

TREATMENT OF FUNCTIONAL SYMPTOMS BY MANIPULATION OF INTESTINAL FLORA WITH ANTIBIOTICS IN DISORDERS OF INTESTINAL FUNCTION

GR CORAZZA, M DI STEFANO

I Department of Internal Medicine, University of Pavia, IRCCS “S.Matteo” Hospital, Pavia, Italy

The metabolic activity of intestinal flora may have a relevant role in the pathophysiology of symptoms of functional bowel disorders, a group of conditions characterized by the presence of an alteration of bowel habit frequently accompanied by bloating, abdominal discomfort or pain and flatulence. These symptoms may be associated with an increased fermentation process at bowel level: when non-absorbable carbohydrates introduced with the diet reach colonic flora, an increase in fermentation occurs and water, short-chain fatty acids and many different gases, namely carbon dioxide, hydrogen, methane, hydrogen sulphide, are produced. A portion of these gases, proportional to total production, is absorbed by the intestinal mucosa and, through the blood circulation, reaches the lungs and is excreted with expired air, thus representing a reliable tool for the evaluation of the extent of colonic fermentation¹. In a group of functional patients suffering from relevant bloating, we recently measured breath hydrogen excretion after the oral administration of lactulose, a non-absorbable sugar². The group of bloating patients showed a significantly higher mean breath hydrogen excretion than a group of healthy volunteers, suggesting that an increase in fermentation may have a role in the pathophysiology of this symptom. However, intraluminal short-chain fatty acids could also be responsible for the occurrence of other abdominal symptoms: in fact, an increased production of short-chain fatty acids through the induction of rapidly propagated, high-pressure waves propelling colonic content extremely effectively may result in both pain and diarrhoea³.

However, an increased intestinal gas production does not characterize all bloating patients and a wide overlap between patients and healthy volunteers is detectable², confirming that intestinal gas production is crucial in a subgroup of bloating patients but is not the only factor determining bloating onset.

In fact, in patients suffering from irritable bowel syndrome, defective gas management and expulsion was recently shown, suggesting that an alteration of motor activity at intestinal level may be responsible for intraluminal gas accumulation and bloating onset⁴. Alteration of visceral sensitivity may also play a role in the pathophysiology of bloating in the group of patients with normal intestinal gas production. We have recently shown that in functional patients with relevant bloating but normal intestinal gas production the induction of colonic fermentation by oral administration of lactulose is responsible for reducing the discomfort threshold to mechanical distention of the rectum⁵, suggesting the presence of hypersensitivity to colonic fermentation in this subgroup of patient.

On the basis of these results, therefore, the modulation of the metabolic activity of colonic flora may represent an interesting therapeutic strategy aimed at improving abdominal symptoms in the subgroup of patients with hyperproduction of intestinal gas.

Lectures

In fact, no significant effect should be expected after the modulation of intestinal flora in the subgroup of patients showing normal intestinal gas production. In a double-blind, placebo-controlled trial, the effect of neomycin on symptom severity and intestinal gas production in a group of irritable bowel syndrome was recently evaluated ⁶ and an improvement of a cumulative symptom score, derived by assessing abdominal pain, constipation and diarrhoea, was shown. Other symptoms such as bloating or flatulence were not evaluated, thus providing only partial information on the effectiveness of this therapeutic approach.

On the contrary, the administration of rifaximin proved to be significantly more effective than charcoal in the reduction of both breath hydrogen excretion and severity of flatulence in a group of functional patients ². Moreover, the variation in breath hydrogen excretion significantly correlated with the variation in flatulence, confirming the close relationship between intestinal gas production and the severity of this symptom, at least in one subgroup of patients ⁷.

REFERENCES

1. Levitt MD, Donaldson RM. Use of respiratory hydrogen (H₂) excretion to detect carbohydrate malabsorption. *J Lab Clin Med* 1970;75: 937-945.
2. Di Stefano M, Strocchi A, Malservisi S, Veneto G, Ferrieri A, Corazza GR. Non-absorbable antibiotics for managing intestinal gas production and gas related symptoms. *Aliment Pharmacol Ther* 2000; 14:1001-1008.
3. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. *Gastroenterology* 1986;91:100-107.
4. Serra J, Azpiroz F, Malagelada JR. Impaired transit and tolerance of intestinal gas in the irritable bowel syndrome. *Gut* 2001;48:14-9.
5. Di Stefano M, Miceli E, Missanelli A, Mazzocchi S, Corazza GR. Hypersensitivity to colonic gas in the pathophysiology of symptoms in functional patients. *Gastroenterology* 2004; 126(Suppl 2): A378.
6. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomised, placebo-controlled study. *Am J Gastroenterol* 2003;98:412-419.
7. Levitt MD, Furne J, Olsson S. The relation of passage of gas and abdominal bloating to colonic gas production. *Ann Intern Med* 1996;124:422-424.

MANAGEMENT OF FUNCTIONAL ABDOMINAL PAIN IN CHILDREN

C DI LORENZO

Children's Hospital of Columbus The Ohio State University, Columbus, OHIO, USA

A child who chronically complains of abdominal pain is often a formidable challenge; although the symptom usually indicates a benign problem, the parents may be terribly worried, the child may be in distress, the practitioner may be concerned about ordering tests to avoid missing serious occult disease, and the family may be enmeshed in psychosocial complexities. Management of this problem can be time consuming and frustrating. Yet, in only a small number of such children is the abdominal pain caused by an underlying organic disease. In most, the pain is functional - that is, without demonstrable evidence of a pathologic condition, such as an anatomic, metabolic, infectious, inflammatory, or neoplastic disorder.

A rational management of this disorder is often challenging, due to the lack of objective diagnostic criteria and unclear pathogenesis. As a consequence, there are no specific, universally effective therapies. The child with functional abdominal pain is best evaluated and treated in the context of a biopsychosocial model of care. Although psychological factors do not help the clinician distinguish between organic (disease-based) and functional pain, it is important to address these factors in the diagnostic evaluation and management of these children.

Education of the family is an essential part of treatment. The family and the patient need to be reassured that the physician believes that the symptoms are "real" and that an organic or progressive disease is not present. An extensive explanation of the nature of the disorder should be given discussing the problem as a common diagnosis and not just an exclusion of an organic disease. A comprehensive but easily understandable description of the nature of "functional" disorders should be attempted. It may be helpful to explain that chronic abdominal pain is a common symptom in children and adolescents, yet few have a disease. Functional abdominal pain can be likened to a headache, a functional disorder experienced at some time by most adults, which very rarely is associated with serious disease. It is important to provide clear and age-appropriate examples of conditions associated with hyperalgesia, such as a healing scar, and manifestations of the interaction between brain and gut, such as the diarrhoea or vomiting children may experience during stressful situations (eg, before school examinations or important sports competitions).

It is recommended that reasonable treatment goals be established with the main aim being the return to normal function rather than the complete disappearance of pain. The family should be discouraged from reinforcing the symptoms by allowing the child to miss school and leisure activities. Patients with perceived low self-worth and academic competence may find the relief of responsibility as a benefit of the pain experience; meanwhile patients with adequate perception of their self-worth may find it discouraging. Return to school can be encouraged by identifying and addressing obstacles to school attendance. Behaviour alternative to assuming the sick role should be encouraged and reward-

ed. Patients should be encouraged to discuss perceived triggering factors. Results suggest that coping-skill interventions for children with chronic abdominal pain should target reductions in passive coping and consider the potential benefits of accommodative coping strategies. Due to the high index of symptomatic success with reassurance, medications are not necessary for every patient with functional abdominal pain. Drug therapy should only be recommended for patients with symptoms interfering with satisfactory quality of life.

Medications for functional abdominal pain are best prescribed judiciously, as part of a multifaceted individualized approach to relieve symptoms and disability. It is reasonable to consider the time-limited use of medications that might help to decrease the frequency or severity of symptoms. Treatment might include acid reduction therapy for pain associated with dyspepsia, antispasmodic agents, smooth muscle relaxants, or low doses of psychotropic agents for pain or nonstimulating laxatives or antidiarrhoeals for pain associated with altered bowel pattern. Few well designed studies have addressed pharmacologic or behavioural interventions in children with pain predominant functional disorders. Peppermint oil (*Mentha piperita*), which is commonly found in many over-the-counter preparations for IBS has long been recognized as a spasmolytic agent that relaxes gastrointestinal smooth muscle relieving pain. A placebo controlled study showed overall improvement in children with IBS who used peppermint oil. A double-blind, placebo-controlled trial of famotidine was conducted in 25 children with abdominal pain and dyspepsia. Among the different variables evaluated, only the global evaluation suggested that there was a benefit of famotidine over placebo. Two RCTs evaluated the efficacy of a cognitive-behavioural program and a cognitive-behavioural family intervention for the treatment of nonspecific abdominal pain. In the first study, results showed that both the experimental and the control groups had decreased levels of pain. However, the treated group improved more quickly, the effects generalized to the school setting, and a larger proportion of subjects were completely pain-free by 3 months' follow-up. In the second study, the children and mothers who were taught coping skills had a higher rate of complete elimination of pain, lower levels of relapse at 6 and 12 months' follow-up, and lower levels of interference with their activities as a result of pain, and parents reported a higher level of satisfaction with the treatment. After controlling for pretreatment levels of pain, children's active self-coping and mothers' caregiving strategies were significant independent predictors of pain behaviour after treatment. In a recent open label study of children using citalopram for treatment of functional abdominal pain, 84% were found to benefit from the drug. Citalopram was generally well tolerated. Ratings of abdominal pain, anxiety, depression, other somatic symptoms, and functional impairment all improved significantly over the course of the study compared with baseline.

REFERENCES

1. Di Lorenzo C, Colletti RB, Lehmann HP, et al. Chronic Abdominal Pain In Children: a Technical Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:249-261.
2. Walker LS, Smith CA, Garber J, Claar RL. Testing a model of pain appraisal and coping in children with chronic abdominal pain. *Health Psychol* 2005;24:364-74.
3. Kline RM, Kline JJ, Di Palma J, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. *J Pediatr* 2001;138:125-128.
4. See MC, Birnbaum AH, Schechter CB, Goldenberg MM, Benkov KJ. Double-blind, placebo-controlled trial of famotidine in children with abdominal pain and dyspepsia: global and quantitative assessment. *Dig Dis Sci* 2001;46:985-992.
5. Sanders MR, Rebetz M, Morrison M, et al. Cognitive-behavioral treatment of recurrent nonspecific abdominal pain in children: an analysis of generalization, maintenance, and side effects. *J Consult Clin Psychol* 1989;57:294-300.
6. Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: a controlled comparison of cognitive-behavioral family intervention and standard pediatric care. *J Consult Clin Psychol* 1994;62:306-314.
7. Campo JV, Perel J, Lucas A, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 2004;43:1234-42.

Lectures

SYMPTOMATIC MANIFESTATIONS OF DIARRHOEAL ILLNESS

RC SPILLER

Wolfson Digestive Diseases Centre, University Hospital, Nottingham, UK

Defining diarrhoea

Physiological definition

The pathophysiology of diarrhoea usually involves an imbalance of absorption and secretion so that stool weight exceeds 200-250g/day. This is usually accompanied by increased stool frequency and water content. Although increased bowel movements (>3/day) has often been used to define diarrhoea, this depends on many factors including work and meal patterns and does not correlate with whole gut transit nor with stool form. Indeed some patients describe increased frequency and even urgency, when what they are passing are small hard stools associated with slow transit and excessive water absorption.

Normal stool weights vary widely throughout the world from 100g/day in the United States to 311g/day in India and 470g/day in Uganda, depending on different intake of dietary nonstarch polysaccharide and also to differences in the gut microbial flora and these need to be taken into account when setting the upper limit of normal stool weight.

Patients' definition

84% of young Americans define diarrhoea as loose/watery stools, 27% urgency, 26% frequent stools, and 24% abdominal discomfort. Similar findings were reported in the UK where the majority of respondents rated a single soft stool as diarrhoea, whereas only a third accepted an increased frequency of defecation.

Proposed definition and its application in clinical practice

These considerations therefore suggest that diarrhoea is best defined as loose or watery stools. This definition can be made less subjective and more applicable to normal clinical practice by using the Bristol stool form score which correlates reasonably well with whole gut transit time¹. Patients often recalled greater bowel frequency than the prospective diary record reveals. Patient diaries are a useful tool avoiding confusion and defining an individual's bowel habits more objectively and allowing better communication between doctor and patient.

Stool Viscosity and Water Content

The sensation of loose stools originating in the extremely sensitive anal canal receptors, depends on stool viscosity, which is in turn strongly influenced by stool water content which normally lies within a narrow range, 70-75%. Water content averages 70-73% in normal subjects and 78-79% in those with functional/idiopathic diarrhoea respectively, however these apparently small variations result in a marked decrease in stool viscosity. When water content is below 70% most of the water is then tightly bound or within bacterial cells and not freely available. Once the water content rises above 70%, further small increases in water content result in relatively large decreases in stool viscosity.

Transit

Most studies of patients with diarrhoea-predominant IBS or functional diarrhoea show a tendency to accelerated small and large bowel transit which correlates inversely with stool frequency ($r = -0.44$) and with daily stool weight ($r = -0.63$)². Healthy males have faster transit than females, associated with increased stool weights and greater responsiveness to dietary fibre. Accelerated transit is associated with increased propagated contractions, particularly the high amplitude propagated contractions (HAPCs), which are increased in frequency and velocity in patients with functional diarrhoea particularly after meals³. HAPCs in D-IBS often precede defecation and are associated with crampy pains and desire to defecate. Chey et al stimulated HAPCs in patients with D-IBS with cholecystokinin and a high-calorie meal under laboratory conditions⁴. Over 90% of pressure waves coincided with abdominal pain or cramps, whereas no similar symptoms nor associations were found in their healthy controls. Scintigraphic studies confirm exaggerated propulsion of stool through the descending colon following meals in patients with functional diarrhoea³, associated with an increase in propagated but not nonpropagated contractions. The lack of mixing and hence retarding contractions may account for the urgency associated with loose stools.

Frequency, Urgency and Incontinence

Normal bowel frequency varies widely but 95% of the normal UK population pass between 3 stools per day to 3 per week². D-IBS patients entering clinical trials are reported as having 2.7 (0.5-5.7) mean (95% CI) stools per day. For many patients, urgency is their most bothersome symptom and the fear of losing continence dominates their lives. Indeed in one clinical trial the feature which correlated best with global improvement was reduction in urgency⁵. Incontinence in patients with diarrhoea was reported in one study to be 20% in those who had consulted a doctor with symptoms compared with just 6% in those who had not, suggesting that this is one symptom that drives people to consult. Frequent incontinence however indicates the need for structural evaluation of the anal sphincter.

REFERENCES

1. Heaton KW, O'Donnell LJ. An office guide to whole-gut transit time. Patients' recollection of their stool form. *J Clin Gastroenterol* 1994;19:28-30.
2. Cann PA, Read NW, Brown C, Hobson N, Holdsworth CD. Irritable bowel syndrome: relationship of disorders in the transit of a single solid meal to symptom patterns. *Gut* 1983;24:405-11.
3. Bazzocchi G, Ellis J, Villanueva-Meyer J, Reddy SN, Mena I, Snape WJ, Jr. Effect of eating on colonic motility and transit in patients with functional diarrhea. Simultaneous scintigraphic and manometric evaluations. *Gastroenterology* 1991;101:1298-306.
4. Chey WY, Jin HO, Lee MH, Sun SW, Lee KY. Colonic motility abnormality in patients with irritable bowel syndrome exhibiting abdominal pain and diarrhea. *Am J Gastroenterol* 2001;96:1499-506.
5. Lembo T, Wright RA, Bagby B, et al. Alosetron controls bowel urgency and provides global symptom improvement in women with diarrhea-predominant irritable bowel syndrome. *Am J Gastroenterol* 2001;96:2662-70. ■

MECHANISMS OF DIARRHOEA IN FUNCTIONAL GASTROINTESTINAL DISORDERS

PJ WHORWELL

Department of Medicine, University Hospital of South Manchester, Manchester, UK

The acute diarrhoea that is associated with gastrointestinal infections is easy to recognise and hardly needs definition. Chronic can be quantified in terms of stool frequency, consistency or volume and has a variety of causes which have been the subject of a recent excellent review¹. The diarrhoea that accompanies irritable bowel syndrome (IBS) is much more difficult to define as it is variable, may alternate with constipation and is often perceived differently by different individuals.

The pathophysiology of functional diarrhoea is poorly understood with disturbances of motility and visceral sensation undoubtedly playing a role². However, other factors such as central processing, inflammation, genetics, diet and psychological status can also contribute to the overall phenotype. This discussion will confine itself to the role of food allergy and intolerance, stress, gender and altered gastrointestinal bacterial colonisation.

Irritable bowel syndrome (IBS) patients often experience an exacerbation of symptoms with food which leads them to conclude that they have a dietary allergy or some form of food intolerance³. There is however, little evidence to support the role of true IgE mediated reactions to food in IBS except possibly in a small subgroup of patients with atopy. Exclusion diets have been shown to be helpful especially in diarrhoea predominant IBS (D-IBS) but are cumbersome and patients find them very hard to follow and adhere to. Alternatively, the simple exclusion of cereal fibre and bran can lead to an improvement in a worthwhile proportion of patients. Recently the role of IgG antibodies to food in IBS has been evaluated in a clinical trial comparing a diet based on the IgG food antibody profile with a sham diet. The real diet resulted in a significant improvement in symptoms although this observation needs confirming in further studies.

Stress unquestionably makes the symptoms of IBS worse although its role in causation of the disorder is much more controversial. Corticotrophin releasing factor (CRF) is the centre of much attention as it is intricately involved in mediating the reaction to stress and has many effects both central and peripheral. Administration of CRF results in the stimulation of a variety of gastrointestinal physiological events and antagonism of CRF is a potential target for future therapeutic approaches to IBS⁴. Stress also has an effect on autonomic function and visceral sensation which is also particularly important in D-IBS.

Serotonin (5HT) can be released in response to a wide range of stimuli ranging from stress to mechanical stimulation of the gut and is involved in gastrointestinal motility and secretion⁵. Carcinoid syndrome is a good demonstration of the role of serotonin in the pathogenesis of diarrhoea and elevated levels of circulating 5HT have been demonstrated in D-IBS providing a rational basis for the therapeutic use of serotonin antagonists in this subgroup of IBS patients.

The notoriously poor response of many patients to the currently available medications and the observation that stress exacerbates

the symptoms of IBS, has resulted in a number of behavioural approaches being evaluated in clinical trials with reasonably encouraging results. However, these approaches are time consuming, expensive, vary in their availability and perhaps more importantly are extremely operator dependent. All these issues therefore limit their use to the more refractory patients seen in referral centres. IBS is more common in females and this may be because they are more susceptible but an alternative explanation is that males might be protected in some way. Most women with IBS experience a peri-menstrual exacerbation of their symptoms which could be related to their sex hormone status. However, prostaglandins released at the time of menstruation may also be involved especially as these agents are known to have potent effects on gastrointestinal function. Increased female susceptibility is also supported by the observation that visceral sensitivity varies with the menstrual cycle in IBS subjects and that laxative induced diarrhoea is more likely to lead to rectal sensitisation in females than males. If males are relatively protected from IBS, it could be in some way linked to their sex hormonal status. It is therefore of interest that it has been shown that testosterone and luteinising hormone levels tend to be lower in male subjects with IBS compared to controls. In addition, male trait scores have been shown to be reduced in men with IBS although it is not known whether this is related in any way to their sex hormone status.

Small intestinal bacterial overgrowth (SIBO) has recently been reported to be more prevalent in patients with IBS. Furthermore, symptomatic improvement following treatment with antibiotics has also been described in such individuals. A role for SIBO in the pathogenesis of IBS is a very attractive hypothesis as this situation is known to influence motility, visceral sensitivity, immune activation and could also theoretically be related to the symptom of bloating⁶. However, the data on SIBO are rather preliminary and are largely based on lactulose breath testing which is subject to influence by a range of factors other than bacterial colonisation. In conclusion, it is still not known why some patients with IBS suffer from diarrhoea and others constipation. We are beginning to understand the mechanisms which dictate bowel function, but how they are kept in balance is still far from clear.

REFERENCES

1. Camilleri M. Chronic diarrhea: a review on pathophysiology and management for the clinical gastroenterologist. *Clin Gastroenterol Hepatol* 2004;2:198-206.
2. Quigley EM. Disturbances of motility and visceral hypersensitivity in irritable bowel syndrome: biological markers or epiphenomenon. *Gastroenterol Clin North Am* 2005;34:221-33.
3. Lea R, Whorwell PJ. The role of food intolerance in irritable bowel syndrome. *Gastroenterol Clin North Am* 2005;34:247-55.
4. Sagami Y, Shimada Y, Tayama J, et al. Effect of corticotrophin releasing hormone receptor antagonist on colonic sensory and motor function in patients with irritable bowel syndrome. *Gut* 2004;53:958-964.
5. Gershon MD. Importance of serotonergic mechanisms in gastrointestinal motility and sensation. In: Camilleri M, Spiller RC, editors *Irritable Bowel Syndrome-diagnosis and treatment*. Saunders WB, 2002:95-116.

Lectures

6. Lin HC. Small intestinal bacterial overgrowth: a framework for understanding irritable bowel syndrome. *JAMA* 2004;292:852-8.

POST-INFECTIVE GUT DYSFUNCTION: DIARRHOEA

SM COLLINS

McMaster University, Hamilton, Ontario, Canada

While infection of the gastrointestinal tract may lead to a variety of changes, including functional dyspepsia, this talk will address the development of persistent diarrhoea, or post-infective irritable bowel syndrome (PI-IBS).

PI-IBS occurs in up to 30% of cases following an episode of acute gastroenteritis and indeed gastroenteritis is the strongest risk factor identified to date for the development of IBS. Risk factors include the severity of the acute infection and the absence of vomiting, the presence of psychoneurosis and antecedent stress. There is emerging evidence that genetic factors may also confer susceptibility via dysregulation of cytokine production favoring a pro-inflammatory cytokine profile.

The clinical expression of PI-IBS is invariably one of diarrhoea, although in some cases the symptom profile can become one of alternating diarrhoea and constipation, or simply constipation over time. The pathophysiology of PI-IBS shows rapid intestinal transit, enhanced rectal sensitivity and increased intestinal permeability. The latter may be important in the maintenance of gut dysfunction by permitting exposure to luminal antigen of bacterial or dietary origin. This is supported by the demonstration of increased numbers of inflammatory cells, particularly lymphocytes, in the colonic mucosa. In addition, there is evidence of bile acid malabsorption in these patients. There is also evidence of serotonin-containing entero-endocrine cell hyperplasia. The latter two observations have therapeutic implications.

The management of PI-IBS is as follows. In some cases, exclusion of persistent or concomitant infection is necessary, particularly in cases seen within 3 months of infection. The precipitation of other gastrointestinal problems such as coeliac disease or inflammatory bowel disease should be considered in susceptible patients. Providing the patient with a linkage between the infective episode and the subsequent development of chronic symptoms provides with an explanation and a measure of reassurance. Trial of a lactose free diet is not usually helpful in these patients. Cholestyramine is recommended based on the fact that bile acid malabsorption may be present. Low dose tricyclic antidepressants may also be helpful in patients with troublesome diarrhoea.

5-HT antagonists are rationalized on the basis of documented EC cell hyperplasia. Originally, PI-IBS was thought to have a very good prognosis but recent evidence indicates that more than 50% of patients remain symptomatic at 6 years.

REFERENCES

1. Gwee KA, Leong YL, Graham C, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;44:400-6.
2. Dunlop SP, Jenkins D, Neal KR, Spiller RC. Relative importance of enterochromaffin cell hyperplasia, anxiety, and depression in postinfectious IBS. *Gastroenterology* 2003;125:1651-9.
3. Collins SM, Piche T, Rampal P. The putative role of inflammation in the irritable bowel syndrome. *Gut* 2001;49:743-5.
4. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology* 2003;124:1662-71.

DIARRHOEAL ILLNESS

EJ IRVINE

Division of Gastroenterology

St. Michael's Hospital, University of Toronto, Toronto, Canada

Most adults referred to a gastroenterologist for diarrhoeal illness will have persistent or chronic diarrhoea. A careful history is the most important factor in discriminating functional from organic bowel disorders. Red flags, such as blood in the stool or other alarm symptoms, are important to identify patients who warrant investigation but do not rule out the presence of a functional disorder. Specific causes of chronic diarrhoea are more prevalent in some populations, partly determined by the geographic setting, race or ethnicity and socioeconomic status. The most frequent in developed countries are irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), coeliac sprue, chronic infections, and idiopathic diarrhoea. In developing countries, chronic bacterial and parasitic infections are widespread, but may also occur in the presence of HIV infection, while functional disorders, IBD, and malabsorption are also common. This discussion will focus on when to suspect and test for important organic disorders.

Clinicians should obtain a history of stool frequency, volume and consistency, description of stool, timing (after meals, night time) as well as any 'red flags' (e.g. bleeding, family history of cancer, weight loss). Medications taken, over the counter medications, prior GI surgery and diet (high fructose, high fiber, artificial sweeteners, wheat etc.) are particularly important in sorting out causes of chronic diarrhoea. A physical examination, including a digital rectal exam is required, but is often normal. An algorithm for investigating patients presenting to a tertiary center with diarrhoea should include stool assessment (culture, *C. difficile*, white blood cells), complete blood count, examination for nutritional deficiency (iron, albumin) and inflammation (CRP, ESR or faecal calprotectin). In those with a high pretest probability of coeliac sprue (e.g. diabetics, siblings of index cases), a specific antibody test is worth performing. Breath testing may be useful to diagnose disaccharidase deficiency or fructose malabsorption. Colonic imaging-whether a limited flexible sigmoidoscopy in patients under

age 40 years with rectal bleeding and a high probability of a local distal cause or a full ileocolonoscopy in patients over age 50 years, with a positive family history of colorectal cancer or with other alarm features should be undertaken. Colonic biopsies, if endoscopic imaging is done, should be obtained, although they do not always contribute to the diagnosis. They are useful to rule out microscopic colitis. Small intestinal imaging should be undertaken when nutritional deficiencies are present and abdominal and/or pelvic ultrasound may be necessary to examine the ovaries when pain is a major accompanying symptom. A trial of therapy, such as antibiotics for small bowel bacterial overgrowth or bile salt binders for bile acid malabsorption may be worthwhile. However, therapies are best directed to the primary diagnosis.

REFERENCES

1. Vanner SJ, Depew WT, Paterson WG, et al. Predictive value of the Rome criteria for diagnosing the irritable bowel syndrome. *Am J Gastroenterol* 1999; 94:2912-2917.
2. Talley NJ. When to conduct testing in patients with suspected irritable bowel syndrome. *Rev Gastroenterol Disord* 2003;3 Suppl 3:S18-S24.
3. Nielsen OH, Vainer B, Schaffalitzky de Muckadell OB. Microscopic colitis: a missed diagnosis? *Lancet* 2004;364:2055-2057.
4. Wildt S, Norby RS, Lysgard MJ, Rumessen JJ. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. *Scand J Gastroenterol* 2003;38:826-830.
5. Buning C, Genschel J, Jurga J, et al. Introducing genetic testing for adult-type hypolactasia. *Digestion* 2005;71:245-250.
6. Midhagen G, Aberg AK, Olcen P, et al. Antibody levels in adult patients with coeliac disease during gluten-free diet: a rapid initial decrease of clinical importance. *J Intern Med* 2004;256:519-524.
7. Cabrera-Abreu JC, Davies P, Matek Z, Murphy MS. Performance of blood tests in diagnosis of inflammatory bowel disease in a specialist clinic. *Arch Dis Child* 2004;89:69-71.

MECHANISMS OF ANORECTAL PHYSIOLOGY IN DIARRHOEAL ILLNESS

G BASILISCO

Gastroenterology Unit, IRCCS Ospedale Maggiore Policlinico, Milan, Italy

The anorectum acts as the final reservoir of the gastrointestinal tract, and allows the voluntary control of defecation. In order to act as a reservoir, the rectum adapts intrarectal pressure upon the arrival of gas or stools, and also informs the brain to find a toilet if necessary (often an urgent need in the case of diarrhoea); the internal anal sphincter relaxes to allow rectal contents to be sampled by the mucosa of the anal canal, and the external anal sphincter may contract to delay defecation.

In patients with diarrhoea due to an established organic cause, the interest of clinicians in such functional changes is relatively limited because they are mainly concerned with treating the cause of the disease and, when this is effective, bowel habits normalise. However, in patients with diarrhoea unrelated to an identifiable organic cause, clinical interest in understanding the altered functions underlying the symptom is prompted by the hope that this will lead to the more rational and effective treatment of the patients' problem.

The aim of this presentation is to discuss whether the reservoir and sensory functions of the anorectum are altered in patients with diarrhoea-predominant irritable bowel syndrome (D-IBS), the most representative and frequent group of patients with "functional" diarrhoea, and to consider the putative causes of these alterations.

In 1990, Prior et al studied a considerable number of IBS patients with diarrhoea or constipation defined on the basis of a detailed history supplemented by diary card data. The rectum was distended at fixed volumes, and it was found that intrarectal pressure was significantly greater in the patients with D-IBS than in those with constipation-predominant IBS or healthy subjects, thus revealing reduced rectal distensibility in the D-IBS patients¹. Similar results can be obtained if the rectum is distended at fixed pressures², a paradigm of distension that nicely demonstrates the abnormal reduction in the functional volume of the rectum of D-IBS patients.

According to the Hill-Maxwell model, the reduced rectal distensibility in D-IBS may involve the plasticity of the muscular and connective tissue (passive components), as well as the contractile state of the muscle (active component). The following observations support the important influence of the contractile state of the muscle on rectal distensibility: 1) rectal tone and distensibility can be modulated by meal ingestion, intrinsic reflexes and pharmacologically through mechanisms affecting smooth muscle contractility; 2) the differences in rectal distensibility between the IBS subgroups are inconsistent at the lowest and at the highest level of distension; 3) impaired rectal distensibility in patients undergoing a complete spinal transection normalises after sacral posterior rhizotomy; and 4) changes in gut distensibility depending on the rate of distension involve neuromuscular mechanisms that act regardless of the passive components.

The attribution of the impaired rectal distensibility observed in D-IBS to the active smooth muscle component instead of to the pas-

Lectures

sive components is not just a semantic or technical issue, but provides: 1) a useful conceptual means of explaining sensory abnormalities, such as the frequent complaint of bowel urgency reported by patients with D-IBS; and 2) a peripheral pathogenetic link with most of the ongoing lines of research into the pathogenesis of IBS. Urgency can be considered a rectal symptom because it is evoked by rectal but not colonic distension. Moreover, recent *in vitro* studies have identified the existence of specialised interganglionic laminae endings in the rectum but not in the colon. These structures have appropriate responsiveness for triggering non-noxious rectal sensations in response to distension³. Rectal interganglionic laminae endings respond for the first few seconds of distension (when the smooth muscle is actively contracted), after which the smooth muscle accommodates and there is a reduction in afferent nerve firing. This firing is greater at faster distension rates, and correlates more closely with the increase in muscular force evoked by stretching than with the change in length. On the basis of these findings, increased rectal smooth muscle contraction can be expected to influence the perception of non-noxious rectal sensations. In line with this hypothesis: 1) a meal- or drug-induced increase in rectal tone increases perception and vice versa; 2) a rate-dependent decrease in rectal distensibility increases the frequency of rectal sensations⁴; 3) the urgency thresholds in D-IBS are lower than in constipation-IBS and healthy subjects,¹ and are associated with impaired rectal distensibility² and 4) rectal sensations are time-related with reflex rectal contraction during isobaric distension.

If an altered neuromuscular response to distension plays a crucial role in limiting the reservoir function of the rectum and increasing the frequency of rectal sensations reported by D-IBS patients, the next question is: why does it occur? A number of not mutually exclusive scenarios can be considered, including an alteration in 1) the intraluminal milieu; 2) the intramural mediators and 3) the extrinsic (central) modulation.

1) The rectal infusion of bile acids changes the motor response of the human rectum and promotes an urgent desire to defecate, thus providing an interesting and relatively unexplored conceptual model of how a change in the intraluminal milieu may influence anorectal physiology. 2) The rectal mucosa of patients with post-infectious IBS contains an increased number of serotonin-positive enteroendocrine cells and of chronic inflammatory cells⁵ that could release substances increasing muscle contractility. 3) Central nervous system modulation affects anorectal function and may be involved in the changes in rectal distensibility observed in D-IBS: anxiety is a frequent co-morbidity in IBS patients and has been shown to be associated with a diarrhoea-predominant bowel habit, impaired rectal distensibility and complaints of urgency.

In conclusion, an abnormal neuromuscular response of the rectal wall to distension can limit the reservoir function of the rectum and induce the perception of urgency at small distension volumes. This peripheral dysfunction provides a useful pathogenetic link to research into functional diarrhoeal illness and may represent a target for treatment.

REFERENCES

1. Prior A, Maxton DG, Whorwell PJ. Anorectal manometry in irritable

bowel syndrome: differences between diarrhoea and constipation predominant subjects. *Gut* 1990;31:458-462.

2. Basilisco G, Paggi A, De Marco E. Objective correlates of the symptom of bowel urgency in patients with irritable bowel syndrome. *Gastroenterology* 2005;128:A-110.
3. Lynn PA, Olsson C, Zagorodnyuk V, et al. Rectal intraganglionic laminae endings are transduction sites of extrinsic mechanoreceptors in the guinea pig rectum. *Gastroenterology* 2003;125:786-94.
4. Corsetti M, Cesana B, Bhoori S, Basilisco G. Rectal hyperreactivity to distension in patients with irritable bowel syndrome: role of distension rate. *Clin Gastroenterol Hepatol* 2004;2:49-56.
5. Gwee KA, Leong YI, Graham JC, et al. The role of psychological and biological factors in postinfective gut dysfunction. *Gut* 1999;44:400-406.

CLINICAL PRESENTATION OF DIARRHOEA IN FUNCTIONAL BOWEL DISORDERS

MJG FARTHING

St George's, University of London, London, UK

Functional diarrhoea, which by definition cannot be explained by structural or biochemical abnormalities, may occur as part of the symptom cluster known as the irritable bowel syndrome (IBS) or as a solitary symptom when it is designated as functional diarrhoea¹. However, functional bowel disorders in which diarrhoea is a dominant symptom are not discreet entities but are generally part of symptom complexes² which may include other gastrointestinal and non gastrointestinal symptoms³.

The term 'diarrhoea' means different things to different people. It may be used to describe an increase in stool frequency or to include an increase in stool frequency and an increase in stool liquidity. It is important to always put actual bowel frequency into the local geographic context and to place more emphasis on changes in bowel habit from the norm, than the absolute bowel frequency.

There is an additional feature that is widely used clinically to distinguish simple bowel frequency ('pseudo-diarrhoea') from true diarrhoea. This criterion is stool weight (or stool volume). In healthy individuals in developed countries stool weight does not usually exceed 200g/24h.

Diarrhoea and IBS

In 1978 Manning et al were able to identify four symptoms that were more common in IBS than in patients with organic gastrointestinal disease. The four symptoms that emerged as important discriminators were looser stools at onset of abdominal pain, more frequent bowel movement at onset of pain, pain eased after bowel movement and visible abdominal distension. The evolving Rome criteria¹ have stressed the importance of abdominal pain or discomfort as the dominant symptom although change in bowel habit remains intrinsic to the definition. The symptoms that

have been repeatedly shown to distress IBS patients most seriously are abdominal pain and abdominal bloating. However, in diarrhoea-predominant IBS and in alternating- (diarrhoea and constipation) IBS, diarrhoea can be a worrying and troublesome symptom which can have a significant effect on quality of life.

The typical patient with diarrhoea-predominant IBS describes bowel frequency up to 3-4 times daily usually in the early morning, soon after rising from bed. Defaecation may be preceded by cramping abdominal pain and passage of a stool may relieve (temporarily) the pain. Many patients report that defaecation is triggered by eating or drinking; this phenomenon is often interpreted as being a clinical marker of an enhanced gastro-colonic reflex. Some patients will have more significant increases in stool frequency sometimes up to as many as 10-15 stools/24h. Stool frequency in such individuals is usually apparent throughout the day again commonly following a mid-day or evening meal. Characteristically these patients pass very small stools and sometimes only mucus will be passed. Bowel frequencies of this order significantly disrupt patients' lives and in some instances render the individual house bound. Many patients are reluctant to leave home until the "morning rush" is over but some will have a detailed list of available toilets that could be used in an emergency during the journey to work. It is unusual for bowel frequency to continue at night and disturb sleep in functional bowel disorders. Fibre-rich vegetables and pulses may increase bowel frequency but perhaps more commonly increase bloating, discomfort and visible abdominal distension.

Although patients may describe their stools as 'watery', on closer questioning the majority have small pelleted stools that intermittently may also take on a fragmented or "fluffy" appearance. Stool form correlates well with colonic transit time (the less formed the stool, the faster the transit) but less well with stool frequency.

Functional Diarrhoea

Manning makes only passing reference to functional "painless" diarrhoea but a comprehensive definition appears in both Rome I and Rome II criteria¹. The major difference between the diagnostic criteria proposed in Rome I and Rome II, is that in the former, stool weight was included as a criterion whereas in Rome II it was excluded. Opinion has now clearly shifted towards the notion that increased stool weight is an indicator of organic disease until proved otherwise. In Rome I, bowel frequency was quantified to three or more bowel movements/24h whereas in Rome II this criterion was removed. Eliminating this restriction would seem to be appropriate for this functional bowel disorder.

Functional (painless) diarrhoea is less common than diarrhoea-predominant IBS and has not received the same intensity of investigation with respect to its epidemiology, co-morbidity, pathophysiology and management. However, the clinical presentation is in many respects similar to that of diarrhoea-predominant IBS with the major exception that there is no pain or discomfort. If some pain and discomfort does exist from time to time, it will fail to meet the criteria intensity set out in the Rome criteria.

Bowel frequency in functional diarrhoea has a similar severity spectrum to that of diarrhoea-predominant IBS and is often associated with other symptoms such as urgency, occasional incontinence, the sensation of incomplete evacuation and straining at

stool. Patients can experience major disability with these symptoms such that like diarrhoea-predominant IBS, they may be phobic of leaving the house or not having close proximity to a toilet. In patients with severe symptoms, the intense bowel frequency can seriously affect their ability to form relationships because of the concerns about disruption of social events and in some the fear of incontinence, particularly during physical intimacy.

Nocturnal bowel frequency does occasionally occur in functional diarrhoea but again this should be considered an alarm symptom to promote further investigation and to confidently exclude an organic cause.

The relationship of diarrhoea symptoms to psychological factors continues to be a challenge for clinicians and investigators concerned with the aetiology and pathogenesis of functional bowel disorders⁴.

Although early reports on IBS prognosis was rather pessimistic more recent data indicate that the future may not be so bleak. During a 12 month period 38% of sufferers can be expected to lose or notice a significant decrease in their symptoms while 9% will acquire new symptoms or experience a return of previous symptoms. Longer-term follow up revealed that 2-18% developed more severe symptoms, 30-50% remained unchanged while the remainder improved or their symptoms resolved altogether⁵.

REFERENCES

1. Thompson WG, Longstreth GF, Drossman DA, Heaton KW, Irvine EJ, Muller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45 (Suppl II):II43-II47.
2. Farthing MJG. Irritable bowel, irritable body, irritable brain? *BMJ* 1995;310:171-5.
3. Whorwell PJ, McCallum M, Creed FH, et al. Non-colonic features of irritable bowel syndrome. *Gut* 1986;27:37-40.
4. Drossmann DA, Creed FH, Olden KW, Svedlund J, Toner BB, Whitehead WE. Psychosocial aspects of the functional gastrointestinal disorders. *Gut* 1999;45 (Suppl II):II25-II30.
5. El-Serag HB, Pilgrim P, Schoenfeld. Systematic review: natural history of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19: 861-870.

Lectures

DIARRHOEAL ILLNESS IN PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX DISEASE

F PACE, S PALLOTTA

Department and Chair of Gastroenterology, University Hospital "Luigi Sacco", Milan, Italy

Symptoms of gastro-oesophageal reflux disease (GERD) are very frequently reported in the western Countries, with an overall prevalence of about 20% in the adult USA general population¹. Chronic diarrhoea is also very common, be it organic or functional, with a reported prevalence of 14 to 18% in the USA². If we focus only on functional causes of chronic diarrhoea, symptom clustering analysis has shown that there is an overlapping area between GERD and IBS bigger than expected³: subjects with GERD have IBS (irritable bowel syndrome), and therefore possibly diarrhoea, more frequently than expected, and nearly 40% of the subjects with IBS experience also heartburn. The causes for this increased frequency of association between the two diseases is still unclear. An other cause of associated symptoms of diarrhoeal illnesses and GERD might be iatrogenic; orally administered proton pump inhibitors (PPIs), the most used treatment for GERD, may give rise to diarrhoea⁴, usually reversible after drug withdrawal. Postulated mechanisms of PPI-related diarrhoea are bacterial overgrowth, bile deconjugation, lipids malabsorption, intestinal pH change, interaction with extra-gastric proton pumps and even microscopic colitis development. Interestingly, also the opposite has been described, i.e. that diarrhoeal complaints in patients with comorbid IBS and GERD was relieved after starting PPI therapy. GERD might be associated with an organic cause of chronic diarrhoea, such as coeliac disease, cystic fibrosis, IBD, Zollinger-Elison syndrome, neurological or psychiatric conditions, and alcohol-related problems. In some of these conditions GERD is more frequent than expected by chance. Finally, diarrhoea might occasionally develop in some GERD patients undergoing antireflux surgery⁵; the incidence of this adverse effect seems not to be related to the appropriateness of indication or kind of technique used for fundoplication, and may be due to iatrogenic lesions, in particular vagal nerve damage.

REFERENCES

1. A Gallup Organization National Survey. Heartburn across America. Princeton, NJ: Gallup Organization, 1988.
2. Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. *Gastroenterology* 1999;116:1464-86.
3. Talley NJ, Dennis EH, Schettler-Duncan VA, Lacy BE, Olden KW, Crowell MD. Overlapping upper and lower gastrointestinal symptoms in irritable bowel syndrome patients with constipation or diarrhea. *Am J Gastroenterol* 2003;98:2454-9.
4. Vanderhof BT, Tahbour RM. Proton pump inhibitors: an update. *Am Fam Phys* 2002;66:273-280.
5. Kozarek RA, Low DE, Raltz SL. Complications associated with laparoscopic anti-reflux surgery: one multispecialty clinic's experience. *Gastrointest Endosc* 1997;46:527-31.

DIARRHOEA DISORDERS IN SUBJECTS WITH FUNCTIONAL DYSPEPSIA

M CORSETTI

Gastroenterology Unit, University Vita-Salute, IRCCS Hospital "San Raffaele", Milan, Italy

Epidemiological surveys suggest that 15-20% of the general population in Western countries experience dyspepsia during the course of one year¹. Functional dyspepsia (FD) is defined as the presence of persistent or recurrent pain or discomfort centered in the upper abdomen for at least 12 weeks in the preceding 12 months, without any evidence of an organic disease that could explain the symptoms¹. Discomfort refers to unpleasant sensations that are not interpreted as pain and which may be characterised by upper abdominal fullness, early satiety, bloating, belching or nausea¹. The pathophysiology of FD symptoms is unclear, but seems to involve a number of mechanisms, including delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distension, abnormal duodenal sensitivity to lipids and acid, unsuppressed post-prandial phasic contractility of the proximal stomach, and altered small bowel motility¹. Moreover dyspepsia symptoms have been associated with sick behaviour, somatisation and neuroticism¹. The pathogenesis of FD is largely unknown but a post-infective origin and genetic predisposition have been suggested: acute onset dyspeptic symptoms after a reported gastroenteric infection were detected in 17% of a series of 400 FD patients¹ and, in another series, an association was found between dyspeptic symptoms and a functional polymorphism of a G-protein subunit¹.

It has been suggested in a recently proposed management algorithm that, after a diagnosis of FD has been determined by clinically excluding patients with alarm symptoms and risk factors suggesting an organic origin of dyspeptic symptoms and symptoms suggestive of gastroesophageal reflux disease, in a population with a high prevalence of *Helicobacter pylori* infection, empirical eradication (if present) and/or trials with acid suppressants (proton pump inhibitors) or prokinetics should be proposed¹. Further investigations that could demonstrate functional gastric alterations (i.e. studies of gastric accommodation to a meal, gastric emptying, gastric sensitivity to distension), and investigational drugs should be reserved for patients with persistent symptoms¹.

The concomitant presence of chronic diarrhoea has been reported in some patients with FD. Diarrhoea is defined as the presence of abnormally liquid or frequent faecal evacuations, and may reflect functional bowel disorders or organic diseases². Depending on its pathophysiological mechanisms, chronic diarrhoea may be inflammatory, osmotic, secretory, factitious, or due to altered gut motility². Diarrhoea may be due to colonic, intestinal, pancreatic or endocrine alterations, the use or abuse of drugs, or a surgical intervention². Some of the causes of chronic diarrhoea have been associated with FD, or could theoretically be related to it. This report describes such causes and their possible underlying mechanisms, and suggests possible treatments in patients with concomitant FD.

A number of studies have suggested an overlap between FD and irritable bowel syndrome (IBS)³, and some have demonstrated no

difference in the prevalence of FD between patients with concomitant diarrhoea- or constipation-predominant IBS. It is not clear what mechanism(s) cause some FD patients to have IBS symptoms but, theoretically, they could share the same pathophysiological mechanisms or be different site manifestations of a single underlying disorder (an irritable digestive tract). Visceral hypersensitivity and motor hyper-reactivity to distension, psychological disturbances, and alterations in the brain-gut axis have been related to the occurrence of symptoms in patients with diarrhoea-predominant IBS³. Their increased sensitivity to distension has been found throughout the gut including the stomach, and the presence of an increased colonic response to a meal has been related to hypersensitivity to duodenal lipid infusion. As suggested in FD, it has been reported that a post-infective symptom onset is more frequent in patients with diarrhoea-predominant than those with constipation-predominant IBS. The presence of psychological disturbances has been associated with the long-term persistence of colonic inflammatory alterations and IBS symptoms after the resolution of an acute gastroenteric infection. The treatment options for patients with concomitant diarrhoea-predominant IBS and FD have not been formally tested, but some studies suggest that treatment aimed at both the dyspeptic and bowel symptoms is possible. The use of acid-suppressants and compounds acting on serotonin receptors improve both dyspepsia and diarrhoea.

On the basis of the pathogenetic hypothesis and pathophysiological mechanisms involved in FD symptoms, it has been suggested that FD also overlaps some organic causes of chronic diarrhoea. Diarrhoea may be a manifestation of the overgrowth of intestinal bacteria. Preliminary data suggest that FD patients may be predisposed to developing small bowel bacteria overgrowth, and this has been related to the presence of altered small bowel motility. Some studies have found that more than 50% of FD patients have altered small bowel motility and that this poorly correlates with dyspeptic symptoms¹, but its possible association with the presence of diarrhoea has not been investigated. Recent studies have demonstrated that small bowel contamination can be reduced by administering prokinetic therapy, which suggests that this therapeutic approach (usually proposed to treat dyspeptic symptoms in FD patients) may also be useful in treating chronic diarrhoea due to small bowel bacterial contamination in FD patients.

On the basis of the hypothesis that the pathogenesis of FD is inflammatory, it can be suggested that chronic diarrhoea in dyspeptic patients may be a consequence of co-existing coeliac disease or lactase intolerance. It has been found that about 20% of coeliac patients have concomitant IBS, and suggested that gluten-induced mucosal inflammation mediates the possible gut dysfunctions underlying IBS symptoms⁴; similar considerations may also apply to FD patients. In the same way, chronic diarrhoea in FD patients could be a manifestation of lactase intolerance. A deficit in the lactase enzyme, which is found in the microvilli of small intestine enterocytes and is responsible for the hydrolysis of dietary lactase, leads to lactose malabsorption and osmotic diarrhoea, and some authors have demonstrated that about 30% of IBS patients are also intolerant to lactose⁴. As acute rotavirus infections in children cause transient lactose intolerance, it has recently been suggested that lactose intolerance may co-exist with post-infective IBS, and

this may also be true of post-infective FD.

Other putative causes of chronic diarrhoea in FD patients are drug abuse and cholecystectomy. Factitious diarrhoea caused by laxative abuse or the spurious addition of water or urine to stool specimens is a common cause of reported chronic diarrhoea in Western populations. As laxative abusers often have a psychopathological history, and FD patients have a high prevalence of such disturbances, factitious diarrhoea may be a cause of chronic diarrhoea in patients with FD.

Chronic diarrhoea occurs in 10% of cholecystectomised patients⁵, and has been found to involve increased gut transit, bile acid malabsorption and an increase in the enterohepatic cycling of bile acids⁵. Cholecystectomy is more frequent in IBS patients than in healthy subjects⁵ and, although it has not been formally investigated, this may also be true of FD patients⁵. The reason for this hypothesis is the fact that dyspeptic symptoms are often confused with those of biliary origin.

Some authors have reported that a number of other diseases causing diarrhoea may be associated with FD, including *Giardia Lamblia* infection, chronic pancreatitis and eosinophilic gastroenteritis. However, in most of these reports, the diseases were actually the cause of dyspepsia and not associated with FD as defined by the Rome II criteria. A recent open study has underlined the possibility that *Giardia Lamblia* infection with co-exists with IBS, but did not suggest a reason for the association. A number of pathophysiological mechanisms underlying the presence of diarrhoea in patients with *Giardia Lamblia* infection have been proposed, including secondary lactose intolerance due to a loss of enzymatic activity in the brush-border of the bowel epithelium, reduced intestinal absorption of nutrients due to parasites layered on the bowel mucosa surface, and the deconjugation of bile salt. Similar considerations may also apply to FD patients.

REFERENCES

1. Tack J, Bisschops R, Sarnelli G. Pathophysiology and treatment of functional dyspepsia. *Gastroenterology* 2004;127:1239-1255.
2. Fine KD, Schiller LR. AGA Medical Position Statement: guidelines for the evaluation and management of chronic diarrhoea. *Gastroenterology* 1999;116:1461-1463.
3. Drossmann DA, Camilleri M, Mayer EA, et al. AGA Technical Review on irritable bowel syndrome. *Gastroenterology* 2002;123:2108-2131.
4. O'Leary C, Wieneke P, Buckley S, et al. Celiac disease and irritable bowel-type symptoms. *Am J Gastroenterol* 2002;97:1463-7.
5. Kraag N, Thijs C, Knipschild P. Dyspepsia – how noisy are gallstones? *Scand J Gastroenterol* 1995;30:411-421.

Lectures

TREATMENT OF DIARRHOEA BY MANIPULATION OF INTESTINAL FLORA

M CAMPIERI, KM LAMMERS, P GIONCHETTI, C MORSELLI,
F RIZZELLO, R TAMBASCO, G BAZZOCCHI
University of Bologna, Bologna, Italy

The observations from several studies do suggest that an altered microflora plays a role in IBS, and further, that the use of substances which modify the intestinal microflora and restore the microbiota balance (that is, antibiotics and probiotics) can be useful in IBS therapy.

Antibiotic treatment

The usefulness of antibiotics in IBS and in particular of non-absorbable molecules, has been suggested by the evidence of bacterial overgrowth in small bowel of IBS patients. In spite of this, the number of clinical trials is poor. Pimentel et al investigated 111 patients with IBS who presented a small bowel overgrowth at the lactulose breath test in 84% of cases. Patients were divided in two blinded groups, one group was treated with neomycin 500 mg per day for 10 days and the other one was treated with placebo for 1 week: 35% of patients in the first group referred an improvement in intestinal symptoms vs 11.4 % of patients in placebo group. The results of this study are questionable because of many methodological limits of the trial¹. Di Stefano et al² examined 34 patients with IBS treated with rifaximin assessing a potential efficacy of this antibiotic in reduction of gas production and related symptoms.

Probiotic treatment

Probiotics have been recently defined as "living organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition"³. This definition emphasizes the importance of a sufficient amount of living microbes in gut and the potential role of probiotics in maintaining and improving microbial balance and in immune-modulation.

Probiotics belong to a heterogeneous group of bacteria producing lactic acid (lactobacilli, streptococci) and bifidobacteria which represent important components of the natural microflora. Other probiotic preparations also include other microbes such as some non-pathogenic strains of *E. coli* and non bacterial micro-organisms such as yeast (*Saccharomyces boulardii*)⁴. For the use in clinical practice, probiotic formulations need to have the following characteristics; probiotic strains must have human origin, must be harmless for the host, resistant to the acid of the stomach, to the digestive process and biliary salts. Probiotics must exert their metabolic activities inside intestinal lumen where they should survive but non persist too long. In addition, they must be resistant to manufacturing process maintaining their benefic properties⁵.

In spite of interesting premises, there are only a few clinical trials about the use of probiotics in IBS and the results are controversial. Twelve trials were published up to 2001 and 14 different probiotic preparations were tested. On the whole 1371 patients were studied. In 10 of these trials at least one intestinal symptom improved and the entity of the improvement was statistically significant. In the other 2 studies there was no difference between

placebo and probiotics. A positive result was obtained in 4 trials using a single species of Lactobacillus (*L. plantarum* or *L. acidophilus* LB), in 2 trials using a single species of *E. faecium* and in 4 studies using a mixture of different strains (*E. faecalis*, *E. coli*, Bacteroides and lactic acid bacteria). No beneficial effects were found in trials using *L. acidophilus* NCFM, *L. helveticus* and sterile mixture of lactobacilli and *E. coli*⁶.

In the last few years, further studies have been published employing a new probiotic preparation, VSL#3, a mixture of 8 different viable lyophilized bacterial strains (*Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium infantis* and *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei* and *Lactobacillus bulgaricus*), highly concentrated (300 billions of bacteria/g) and useful in IBD treatment⁷⁻¹⁰. Bazzocchi et al examined 42 patients who fulfilled the Rome II diagnostic criteria for the diagnosis of diarrhoea-predominant IBS. VSL#3, 3 g/day, was administered in the morning and in fasting conditions for 20 days; all patients underwent to manometric examination, while just 10 patients collected a stool sample at the 1st and last day of treatment. At the end of the study, 81% of patients referred a significant reduction in symptoms. After VSL#3 treatment visceral perception decreased and colon motility normalized as evaluated by motility index (MI) and high amplitude propagating contractions (HAPC) after mechanical colon distension. Bacterial strains within the probiotic preparation VSL#3 were detected in patients' faeces after treatment in addition to some enzymatic activities characteristic of lactobacilli. Microbiological evaluation further reported a reduction of urease activity as an expression of a reduced metabolic activity of the resident flora and a successful probiotic colonization. In another trial, Bazzocchi et al¹¹ studied 68 patients with diarrhoea-IBS (n=49) or functional diarrhoea (n=19). Both group of patients fulfilled the Rome II diagnostic criteria. Only patients with 3 or more daily bowel movements were enrolled. In contrast with IBS patients, patients with functional diarrhoea did not present abdominal pain. Patients assumed VSL#3 (2 sachets/day) for 20 days and recorded all their symptoms for 1 week before treatment (T0) and during the last week of treatment (T1). Fifteen patients underwent colonic motility examination before and after the treatment and their faecal samples were analyzed at T0, T1 and 15 days after suspension of VSL#3 (T2). VSL#3 improved symptoms in most patients in terms of frequency of evacuations, stool consistency and appearance, degree of abdominal pain, urgency and bloating. Effective colonization of large bowel and change in faecal concentration of principle bacterial strains occurred, urease and other enzymatic activities were modified, contractile response and visceral perception to mechanical colonic stimulation were reduced during the treatment¹¹. At the end of the study, 77.5% of IBS patients and 73.6% of FD patients referred significant relief of symptoms; besides, at the end of the study Rome II diagnostic criteria were not met any more in 69.4% and 63.2% of the IBS and functional diarrhoea patients, respectively. In a recent study, Kim et al¹² performed a randomized, controlled trial of VSL#3 versus placebo, designed to study the effect of this probiotic preparation on gut transit and symptoms such as abdominal pain, flatulence, urgency and bloating. Their results demonstrated that VSL#3 significantly reduced abdominal bloating when

compared to placebo, but had no effect on the other parameters tested, that is, small bowel or colonic transit, bowel dysfunction, pain, flatulence or urgency.

Discussion

The majority of the clinical trials on probiotics in IBS that were performed in the past few years have some limits and the results are often controversial. Trials lack a prolonged follow-up period and there are too many differences in types of probiotic preparations (in terms of concentration, composition, length of treatment) to draw steady conclusions. For example, it has still to be determined if the efficacy of bacteriotherapy in functional bowel disorders is due to a specific type of probiotic bacterial strain, a particular dosage or a mixture of probiotic bacteria rather than single strain. Furthermore, it is not clear yet whether one of the 3 IBS patient subgroups (that is, patients with constipation, patients with diarrhoea or patients alternating between the two) and/or patients with functional diarrhoea may benefit in different ways from probiotic therapy.

The clinical trials from Bazzocchi et al¹¹ and Kim et al¹² include three important aspects; a homogeneous population, the enrollment of patients with severe symptoms according the Rome II diagnostic criteria, and properties of the probiotic preparation. Bazzocchi et al enrolled patients with functional diarrhoea or diarrhoea-predominant IBS and the two groups were separated throughout the trial and during data elaboration. Patients with mild symptoms and psychological disorders were excluded to avoid interferences in final results. Even if this trial is open and not controlled, it represents one of the first studies that describes a relationship between probiotic treatment, symptom improvement and objective data such as modification of stool composition, enzyme activities and bowel motility. In the study of Kim et al, patients with diarrhoea-predominant IBS were included and randomly received VSL#3 or placebo. In addition to evaluation of symptoms, gastrointestinal transit score were evaluated. In both trials, the authors employed an highly concentrated probiotic preparation; this is a basic aspect as the correct amount of bacteria in bowel seems to be a critical factor for colon colonization and consequent success of bacteriotherapy.

Conclusion

The rationale for using probiotic preparations in the treatment of IBS has been discussed for a long time and is supported by epidemiological and physiologic considerations, by experimental data and by the results of clinical trials. Even if further studies are needed, the concept for the use of probiotics as a potential therapy in IBS is very attractive as probiotics are safe, may be considered as nutritional supplement and may therefore be well accepted by patients.

REFERENCES

1. Pimentel M, Chow EJ, Lin HC, et al. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome: a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol* 2003;98:412-419.
2. Di Stefano M, Strocchi A, Malservis S, et al. Non-adsorbable antibiotics for managing intestinal gas production and gas-related symptoms. *Aliment Pharmacol Ther* 2000;14:1001-1008.
3. Fuller R. Probiotics in human medicine. *Gut* 1991;32:439-442.
4. Campieri M, Gionchetti P. Probiotics in inflammatory bowel disease: new insight to pathogenesis or a possible therapeutic alternative? *Gastroenterology* 1999;116:1246-1249.
5. Salminen S, von Wright A, Morelli L, et al. Demonstration of safety of probiotics- a review. *Int J Food Microbiol* 1998;44:93-106.
6. Hamilton-Miller JMT. Probiotics in the management of irritable bowel syndrome: a review of clinical trials. *Microbial Ecology Health Dis* 2001;13:211-215.
7. Venturi A, Gionchetti P, Rizzello F, et al. Impact on the composition of the faecal flora by a new probiotic preparation: preliminary data on maintenance treatment of patients with ulcerative colitis. *Aliment Pharmacol Ther* 1999;13:1103-1108.
8. Gionchetti P, Rizzello F, Venturi A, et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;119:305-309.
9. Gionchetti P, Rizzello F, Helwig U, et al. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003;124:1202-1209.
10. Mimura T, Rizzello F, Helwig U, et al. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;53:108-114.
11. Bazzocchi G, Almerigi PF, Gionchetti P, et al. Changes in symptoms, distention-stimulated colonic motility and in fecal microbiological features after oral bacteriotherapy in patients with diarrhea-predominant IBS (D-IBS) or with functional diarrhea (FD). *Am J Gastroenterol* 2002;97 (Suppl.):A847.
12. Kim HJ, Camilleri M, McKinzie S, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Aliment Pharmacol Ther* 2003;17:895-904.

Lectures

PHARMACOLOGICAL TREATMENT OF DIARRHOEA IN PATIENTS WITH FUNCTIONAL INTESTINAL DISORDERS

J TACK

Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium

The aim of this presentation is to review the current pharmacological treatment options for chronic diarrhoea and faecal incontinence. Symptomatic pharmacological treatment may be used while (the result of) diagnostic evaluation is pending, or when a diagnostic investigation did not demonstrate a clear cause or a readily treatable underlying cause.

Antidiarrhoeal agents may be classified as intestinal transit inhibitors (opioids, tricyclic antidepressants), intraluminal agents (cholestyramine, medicinal fiber, clays, activated charcoal, bismuth), proabsorptive agents (clonidine), and antisecretory drugs (octreotide). In the treatment of faecal incontinence, increasing stool consistency through anti-diarrhoeal action is a major goal, as formed stool is easier to control than soft or liquid stool.

Exogenous opioid receptor ligands are the most frequently used agents in the treatment of diarrhoea. Diphenoxylate and especially loperamide are preferentially used, as they lack central nervous system effects. Loperamide inhibits peristalsis, slows intestinal and colonic transit times and increases anal sphincter pressures. Tricyclic anti-depressants, which have some anticholinergic and therefore anti-diarrhoeal actions, have traditionally been used in the treatment of irritable bowel syndrome. Antagonists at the 5-HT₃ receptor slow colonic transit time. Clinical studies have established that the 5-HT₃ receptor antagonist alosetron is able to improve stool pattern and to provide relief of pain/discomfort diarrhoea-predominant IBS¹. Due to suspected side-effects of colonic ischemia, the drug is only available in a restricted use program in the U.S., and is unavailable elsewhere.

Racecadotril is an enkephalinase inhibitor, presented as a purely antisecretory agent for the treatment of diarrhoea. Clinical efficacy has mainly been established in acute infectious diarrhoea. Studies in chronic diarrhoea are not available. Several studies have addressed the use of phenylephrine gel in the treatment of faecal incontinence. Through sympathomimetic effects, the drug is able to dose-dependently increase anal sphincter tone, but controlled clinical studies have not been convincing. One study suggested a favourable effect of the use of sodium valproate in patients with faecal incontinence after ileoanal anastomosis².

Up to 50% of patients with chronic idiopathic diarrhoea have bile acid malabsorption, and this is the group of patients that respond best to cholestyramine treatment³. Cholestyramine and related binding resins are able to improve urgency and stool consistency, and to reduce stool frequency and stool weight. Bismuth subsalicylate has been shown to be effective in acute travelers' diarrhoea, but its effectiveness in chronic diarrhoea has mainly been demonstrated in microscopic colitis⁴. Its usefulness in other types of chronic diarrhoea is unproven. Chronic treatment should be avoided as some bismuth may be absorbed and there is a potential risk of encephalopathy.

Bulking agents, such as psyllium, or hydroscopic agents, such as gum agar, are usually used in the treatment of constipation. However, by increasing stool bulk and by absorbing water, they may aid in the treatment of faecal incontinence and mild diarrhoea. These agents do not reduce stool weight and are not suitable for patients with more severe diarrhoea.

In diabetic diarrhoea, efficacy of clonidine, a proabsorptive agent, has been reported⁵. There are probably also motor components to the efficacy of clonidine, as the drug was shown to slow intestinal transit and inhibits colonic tone in health. The drug has an unfavourable side effect profile and there are only anecdotal reports of use of clonidine in chronic diarrhoea of other origins.

The somatostatin analogue octreotide has proven effectiveness in several types of chronic diarrhoea, such as carcinoid diarrhoea, dumping syndrome, short bowel syndrome, chemotherapy-induced diarrhoea and AIDS-associated diarrhoea⁶. Octreotide promote intestinal absorption and inhibits gastric, pancreatic, and intestinal secretion. In consideration of the mode of administration, potential long-term complications and expense, the drug should be considered a third-line agent to be used when other more conventional treatments have failed.

REFERENCES

1. Camilleri M, Northcutt AR, Kong S, Dukes GE, McSorley D, Mangel AM. Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial. *Lancet* 2000;355:1035-40.
2. Kusunoki M, Shoji Y, Ikeuchi H, Yamagata K, Yamamura T, Utsunomiya J. Usefulness of valproate sodium for treatment of incontinence after ileoanal anastomosis. *Surgery* 1990;107:311-5.
3. Wildt S, Norby Rasmussen S, Lysgard Madsen J, Rumessen JJ. Bile acid malabsorption in patients with chronic diarrhoea: clinical value of SeHCAT test. *Scand J Gastroenterol* 2003;38:826-30.
4. Fine KD, Lee EL. Efficacy of open-label bismuth subsalicylate for the treatment of microscopic colitis. *Gastroenterology* 1998;114:29-36.
5. Fedorak RN, Field M, Chang EB. Treatment of diabetic diarrhea with clonidine. *Ann Intern Med* 1985;102:197-199.
6. Farthing MJ. Octreotide in the treatment of refractory diarrhoea and intestinal fistulae. *Gut* 1994; 35(3 Suppl):S5-10.

MANAGEMENT OF DIARRHOEA IN CHILDREN WITH DISORDERS OF INTESTINAL FUNCTION*S AURICCHIO, E MIELE*

Department of Pediatrics, University "Federico II", Naples, Italy

Recently, the Committee on Childhood Functional Gastrointestinal Disorders (FGIDs) provided criteria for defining FGIDs in infancy, childhood, and adolescence for the first time¹. On the basis of these criteria, in pediatric age two conditions can be identified responsible of a functional diarrhoea, the toddler diarrhoea with onset in infancy or preschool years and the diarrhoea-predominant irritable bowel syndrome (IBS), that affects children old enough to provide an accurate pain history¹.

The syndrome described as chronic non specific diarrhoea (CNSD), toddler diarrhoea or the irritable colon syndrome of childhood is the most common cause of chronic diarrhoea without failure to thrive in childhood, yet the pathophysiological mechanisms operating in this condition are largely unknown². Despite the facts that pathophysiology of CNSD is still unclear and the fact that no clear-cut test positively identifies children with CNSD, its history, symptoms, and clinical course are highly typical and, in many cases, enable the diagnosis to be made without additional investigation. Effective management involves dietary interventions and reassurance of parents.

An intermittent diarrhoea, abdominal discomfort, that is relieved by defecation, flatulence and occasional constipation can be characteristic symptoms of IBS. Abnormalities described in children with IBS have included an increased sensitivity (visceral hypersensitivity) and a disturbed contractile response to a meal. There are no specific studies on the pathophysiology of the diarrhoea-predominant IBS³.

CNSD is the leading cause of chronic diarrhoea in an otherwise well child from an industrialized country. There are no specific data about the prevalence of diarrhoea-predominant IBS in school-age children and adolescents. However, population based studies indicate that 6-14% of the adolescent population note symptoms consistent with the IBS⁴.

A recent Italian prospective survey from Miele et al assessed the prevalence and natural history of FGIDs in children using the Rome Criteria. CNSD affected 0.07% of studied population, that represented 3.6% among FGIDs, whereas IBS affected 0.21% of studied population, that represented 10.3% among FGIDs⁵.

Treatment is directed toward symptom reduction. Dietary manipulation may be helpful in some cases. Drug therapy plays an adjunctive role. Several drugs, such as tricyclic antidepressants, have been used for decades for chronic visceral pain and for disordered defecation, but there are only anecdotal reports concerning their use in children. Although diarrhoea in children with disorders of intestinal function is a difficult problem to treat, it is important to stress that there is no significant morbidity associated with it. Functional diarrhoea is not associated in childhood with poor growth, blood in the stools, malnutrition, malabsorption, dehydration, or propensity for later inflammatory bowel disease. In children who are otherwise healthy and growing well, normalizing the diet, including fat intake, while reducing excessive intake of carbohydrates and fluids is indicated. Parents should be reassured that functional diarrhoea improves with these measures alone. In rare instances, further evaluation and/or any kind of medical treatments are needed in children who fail to respond to the dietary changes. CNSD resolves by the time the child starts school. However, it could be hypothesized that there is overlap between this disorder and IBS of childhood and some of those children with a diagnosis of CNSD who have intermittent periods of diarrhoea after starting school may in fact have irritable bowel syndrome.

sured that functional diarrhoea improves with these measures alone. In rare instances, further evaluation and/or any kind of medical treatments are needed in children who fail to respond to the dietary changes. CNSD resolves by the time the child starts school. However, it could be hypothesized that there is overlap between this disorder and IBS of childhood and some of those children with a diagnosis of CNSD who have intermittent periods of diarrhoea after starting school may in fact have irritable bowel syndrome.

REFERENCES

1. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut* 1999; 45 Suppl 2: II 60-8.
2. Walker-Smith JA. Toddler's diarrhoea. *Arch Dis Child* 1980;55:329-30.
3. Van Ginkel R, Voskuil WP, Benninga MA, Taminiou JA, Boeckxstaens GE. Alterations in rectal sensitivity and motility in childhood irritable bowel syndrome. *Gastroenterology* 2001;120:31-8.
4. Hyams JS, Burke G, Davis PM, et al. Abdominal pain and irritable bowel syndrome in adolescents: a community-based study. *J Pediatr* 1996; 129: 220-226.
5. Miele E, Simeone D, Marino A, et al. Functional gastrointestinal disorders in children: an Italian prospective survey. *Pediatrics* 2004; 114:73-78.

Lectures

MECHANISMS OF CONSTIPATION IN FUNCTIONAL DISORDERS

MA KAMM

Physiology Unit, St Mark's Hospital, London, UK

The symptom of constipation encompasses decreased bowel frequency, the need to strain during defaecation, unsatisfied defaecation, a sense of incomplete emptying, hard stools, and pain during defaecation. For some it also encompasses broader symptoms such as bloating and distension. It therefore embraces a mixture of subjective elements, in addition to physiological changes.

Underlying this symptom is a variety of pathogenic mechanisms. These mechanisms include components related to the brain, spinal cord, gut and pelvic floor.

The brain exerts powerful control over large bowel and pelvic floor function. Psychological state has a major impact on bowel function. Introverted individuals have a lower stool frequency and produce less stool than extroverts. Constipation is commonly present in those with depression. Adverse life events, such as abuse and parental loss, appear to play an important causative role in some people. Defaecation can also be voluntarily suppressed. In all these conditions, the brain may play an inhibitory role through extrinsic autonomic pathways to the large bowel. CRF is one of the important central mediators in this process. Measurement of mucosal blood flow can be used to assess the level of activity of this autonomic extrinsic innervation.

Patients with spinal cord injury often experience constipation. Lack of positive extrinsic innervation is clearly important, other factors such as poor mobility and drugs may also play a role. Patients with other neurological diseases, such as multiple sclerosis, also have an excessive incidence of constipation; while this sometimes relates to impaired innervation, behavioural treatments have demonstrated that there is often a reversible component. Abnormal extrinsic innervation, principally diminished parasympathetic drive or excessive inhibitory sympathetic innervation, is thought to underlie the development of acute pseudo-obstruction in patients with non-bowel acute medical problems.

Constipation is a feature of many patients with disorders of visceral muscle and nerve, including patients with chronic pseudo-obstruction. Abnormal pelvic floor function can result in impaired evacuation, and slow large bowel transit. This can serve as a useful focus for behavioural treatment, although the mechanism of action of such treatment is complex and may involve cerebral as well as pelvic floor factors.

After prolonged chronic straining some women develop bulging of the rectal wall at its weakest point, the anterior recto-vaginal septum. A large rectocele can be associated with impaired emptying and the need to digitally assist defaecation.

In patients with decreased bowel frequency there is a decrease in the frequency of high pressure propagated contractions, that is peristaltic movements. Transit can be measured. Assessment of pelvic floor dynamics during attempted defaecation is often subjective and may be poorly reproducible.

Understanding the mechanism underlying constipation will lead to improved therapies. However, sometimes the therapies themselves teach us about factors that contribute to the condition.

REFERENCES

1. Bassotti G, Chiarioni G, Vantini I, et al. Anorectal manometric abnormalities and colonic propulsive impairment in patients with severe chronic idiopathic constipation. *Dig Dis Sci* 1994;39:1558-64.
2. Glickman S, Kamm MA. Bowel dysfunction in spinal cord injury patients. *Lancet* 1996;347:1651-1653.
3. Chiotakakou-Faliakou E, Kamm MA, Roy AJ, Storrie JB, Turner IC. Biofeedback provides long term benefit for patients with intractable slow and normal transit constipation. *Gut* 1998;42:517-521
4. Mason H, Serrano-Ikkos E, Kamm MA. Psychological morbidity in women with idiopathic constipation. *Am J Gastroenterol* 2000;95:2852-7.
5. Wiesel PH, Norton C, Roy AJ, Storrie JB, Bowers J, Kamm MA. Gut focused behavioural treatment (biofeedback) for constipation and faecal incontinence in multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2000;69:240-243.

PELVIC AND RECTAL ALTERATIONS IN CONSTIPATION ILLNESS

FI HABIB

Department of Clinical Sciences University "La Sapienza", Rome, Italy

Normal defaecation requires a normal colonic motility, the perception of sensory stimuli from the rectal wall, pelvic floor and anal canal, an expulsion force and the coordinated function of the pelvic floor to evacuate. Thus constipated patients may have impaired colonic transit (slow transit constipation) and/or pelvic floor dysfunction (obstructed defaecation). Obstructed defaecation is observed in half of the constipated patients, occurring more frequently in females. Evacuation problems often arise during the fourth or fifth decade of life when progressive weakening of the supported tissues takes place.

Impaired defaecation may be due to different mechanisms that may be summarized in the following three groups:

1. Inefficient act of defaecation. Due to disregarded call to stools, impaired rectal sensation, megarectum, impaired expulsion force, altered straining pattern, perineal descent, immobile perineum.
2. Impaired faecal expulsion. Due to pelvic floor dyssinergia, rectocele, enterocele, intussusception, hypertensive anal sphincter.
3. Faeces alterations. Lumpy hard stools, pelletty stools, faecaloma, faecal impaction.

Rectum is a specialized segment with viscoelastic properties to allow significant accommodation to colonic materials. Perception of sensory stimuli from the rectal wall, pelvic floor and anal canal is important for both continence and defaecation. Rectal compliance is the ability of the rectum to adapt to increasing volumes of distension because of its anatomy in the circular and longitudinal muscle layers¹. Altered rectal compliance may result in enhanced or diminished rectal tone, the latter of which may be responsible of hypotonic rectum or megarectum, in particular when associated to elevated sensory thresholds, with the loss of the sense of urgency, faecal impaction and overflow incontinence².

It has been shown that rectal sensitivity is altered in 56% of patients complaining of constipation³, with no relationship with modality of bowel transit, although patients with slow gastrointestinal transit time appear to be more markedly affected.

Pelvic floor dyssinergia (PFD) is described as the paradoxical contraction or failure to relax the external anal sphincter and/or the puborectalis muscle during the straining to defecate. It is observed in a large number of chronic constipated patients, using different diagnostic tests: electromyography of the external anal sphincter, anal manometry and defecography. However the agreement between these different examinations is poor, and the role of dyssinergia of pelvic muscles in affecting rectal emptying, and total and segmental large bowel transit is controversial. Recently PFD has been re-defined according to standardized criteria (Rome II criteria) requiring also the evidence of intrarectal pressure during straining, plus the inability to defaecate at least 40% of the contrast during defecography⁴. A group of patients complaining of

constipation were submitted to defecography and gastrointestinal transit time and the summary of the results are as follow:

- Defecographic patterns of paradoxical contraction or failure to relax of pelvic muscles during evacuation is present in 50% of chronic constipated patients
- In less than half of these patients (19%) it is associated with a poor rectal emptying to make diagnosis of PFD
- A subgroup of patients show incomplete evacuation without pelvic muscle dyssinergia: all these subject had a rectocele larger than 3.5cm, but its prevalence in the group did not differ statistically from the pelvic floor dyssinergia group
- PFD does not affect large bowel transit, which is delayed in patients without pelvic dyssinergia
- Rectal transit is not delayed in pelvic floor dyssinergia
- Intussusception is more frequently observed in patients without pelvic floor dyssinergia, and in patients with complete evacuation.

These observations suggest that: (1) dyssinergia of the pelvic muscles is frequently observed in chronic constipation patients, but criteria for the diagnosis of pelvic floor dyssinergia are met only in a small part of these patients; (2) pelvic floor dyssinergia is a major pathogenetic factor in patients with chronic functional constipation and normal total gastrointestinal transit time; (3) other presumptive defaecographic abnormalities do not have any relationship with gastrointestinal transit time.

Defecography, now evolved to perineography with the opacification of vagina, bladder and small bowel, recognize unsuspected enterocele, particularly in patients previously submitted to hysterectomy. By means of defecography it is possible to measure pelvic floor location at rest and its mobility during squeezing and evacuation thus objectivating the suspicion of descending perineum syndrome⁵.

Rectocele and intra-rectal/anal intussusception are frequent findings in chronic constipation and their surgical repair has been proposed for the treatment of obstructed defaecation syndrome. However it is not established whether rectocele and intrarectal/anal intussusception, *per se*, affect rectal transit and/or emptying and on the other hand rectocele and intra-rectal intussusception are frequent finding also in control subjects⁶.

REFERENCES

1. Keljo DJ, Squires RH Jr. Anatomy and anomalies of the small and large intestine. In: Feldman M, Scharschmidt BF, Sleisenger MH, eds. Sleisenger & Fordtran's Gastrointestinal and Liver disease: Pathophysiology/diagnosis/ management, 6th ed. Philadelphia PA WB Saunders Company, 1998:1419-1436.
2. Meunier P, Mollard P, Marchal J-M. Physiopathology of megarectum: The association of megarectum with encopresis. Gut 1976; 17:224-227.
3. De Medici A, Badiali D, Corazzari E, Bausano G, Anzini F. Rectal sensitivity in chronic constipation. Dig Dis Sci 1989; 5:747-753.
4. Whitehead WE, Wald A, Diamant NE, Enck P, Pemberton, JH, Rao SSC. Functional disorders of the anus and the rectum. In: Drossman DA, Corazzari E, Talley NJ, Thompson WG, Whitehead WE editors. Rome II: the functional gastrointestinal disorders. McLean, VA:

Lectures

- Degnon Associates; 2000, p.483-532.
- Habib FI, Corazziari E, Viscardi A, Badiali D, Torsoli A. Role of body position, gender and age on pelvic floor location and mobility. *Dig Dis Sci* 1992;37:500-505.
 - Shorvon PJ, McHugh S, Diamant NE, Somes S, Stevenson GW. Defecography in normal volunteers: results and implications. *Gut* 1989;30:1737-1749.

CLINICAL PRESENTATION OF CONSTIPATION ILLNESS

D BADIALI

Department of Clinical Sciences, University "La Sapienza", Rome, Italy

Constipation is a symptom reported by patients as infrequent bowel movements, difficult defecation and incomplete evacuation. About 5% of subjects in the general population report fewer than three evacuation/week, 10-18% at least one defecation disturbance (straining, hard stools, a feeling of incomplete evacuation), and <1% report digital evacuation or perineal support during defecation. These symptoms have been shown to be correlated^{1, 2}.

The Rome II diagnostic criteria³ defined constipation as a bowel frequency of fewer than three movements per week **and/or** the presence of at least **two of the following symptoms in more than 25% of defecations**: straining, lumpy or hard stools, a sensation of incomplete evacuation, a sensation of anorectal obstruction/blockage, and manual manoeuvres to facilitate defecation (e.g. digital evacuation, pelvic floor support). On the basis of this standardised definition, constipation affects ~15% of the Western population, but more than 25% define themselves as constipated⁴ and the majority of patients who would otherwise be considered constipated also complain of other abdominal and extra-abdominal symptoms.

Constipation and disorders of intestinal function

The symptoms of altered bowel patterns form part of the definitions of three different but substantially overlapping bowel function disorders: functional constipation (FC), pelvic floor dyssynergia (PFD), and constipation-predominant irritable bowel syndrome (C-IBS)⁵. The main feature of PFD is the evidence of pelvic floor contraction (or lack of relaxation) during attempts at defecation that obstructs rectal emptying; IBS is characterised by the presence of abdominal discomfort/pain associated with the onset of reduced bowel frequency and/or hard or lumpy stools.

Constipation is often associated with abdominal bloating and/or pain, which may also occur in the presence of PFD although no reference is made to it in the definition. Furthermore, many constipated patients (88%) use laxatives, which can cause pain and become one of the pathophysiological mechanisms of symptom

presentation, thus making it difficult to distinguish FC and PFD from C-IBS in clinical practice.

Factor analysis studies have shown that IBS and FC seem to be distinct disorders identified by separate symptom clusters⁶. IBS seems to be defined by the main symptoms of abdominal pain/discomfort relieved by defecation, which is time-related to changes in stool frequency or consistency, whereas straining and a feeling of incomplete evacuation cluster with constipation symptoms (reduced bowel frequency, digitation).

Symptom presentation and altered function

Chronic constipation is usually divided into slow-transit constipation and dyssynergic defecation. The symptoms of constipation may be present in the absence of any clear physiological alteration, and the functional subgroups of constipation significantly overlap in the clinical setting. Furthermore, the symptoms poorly correlate with physiological alterations and those reported by patients do not predict the underlying mechanism. Dyssynergia between abdominal muscle contraction and pelvic floor relaxation is necessary for a diagnosis of PFD, but dyschezia may also be due to hard or pellety stools caused by excessive dehydration during slow colon transit.

A factor analysis study⁷ comparing the symptoms suggesting C-IBS, slow transit constipation and PFD with the functional alterations detected by means of large bowel transit measurements, anorectal manometry and rectal sensitivity tests found that fewer than three bowel movements per week and the lack of a call to evacuate correlate with slow transit, and abdominal discomfort and a feeling of incomplete evacuation with altered sensitivity tests; however, the symptoms suggesting PFD did not correlate with any specific functional alteration.

Abdominal pain in functional constipation

An Italian multicentre survey⁸ of 231 adult patients with chronic constipation showed that 76% reported abdominal pain, the main characteristics of which were cramp-like pain localised in one or more abdominal sites (77%) rather than over a larger abdominal area, and experienced as severe by 11% of the subjects. The patients with and without abdominal pain did not differ in terms of age or the duration of constipation, but there was a gender difference: the female/male ratio was 5:1 among those complaining of pain and 2:1 among those with painless constipation. The severity of the pain also differed between genders, being described as severe by 20% of the females and 3% of the males. The presence of pain was not related to delayed large bowel transit as transit time was abnormal (>96 hours) in 51% and normal in 49% of the subjects with painful constipation.

The Rome II diagnostic criteria refer to IBS when the onset of abdominal pain is strictly time-related to a bowel change. Although pain and altered bowel movements may not be time-related in constipated patients reporting abdominal pain, it is well known that discomfort can be relieved or aggravated by defecation, and defecation is attempted with the aim of alleviating the pain.

So patients with constipation and abdominal pain not time-related with bowel alterations, are more likely to be viewed as FC as opposed to IBS. Abdominal pain arising after several days of no stools and relieved or aggravated by defecation can be interpreted

ed as being secondary to faecal distension, and also this condition is more likely to be considered FC.

Abdominal pain can also induce patients to try to defecate (some repetitively and with the aid of laxatives or enemas) in a vain attempt to relieve the pain, a condition that configures obsessive-compulsive behaviour rather than IBS or FC.

Abdominal pain can occur in patients with PFD and other evacuation disorders obstructing defecation as the pain caused by faecal retention and stasis in the rectum and colon may mimic that of IBS. The fact that abdominal pain disappears after the successful treatment of faecal retention in patient subgroups such as children indicates that faecal retention leading to rectal and colon distension may play a role in the origin of abdominal pain. However, the close time-relationship between the disappearance of abdominal pain after bowel movement is common in children with faecal retention but not as frequent in adults with functional constipation.

An additional feature characterising IBS is the intermittent nature and variable severity and clinical expression of the disturbances: IBS may involve symptom-free periods and variations in bowel patterns, unlike the more stable clinical presentation of FC.

Conclusion

Constipation symptoms are present in different syndromes of altered bowel function, thus making it objectively difficult to distinguish constipation-predominant IBS from FC and PFD with abdominal pain. A critical evaluation of the symptoms (particularly of the different relationships between bowel patterns and abdominal pain) and use of some simple tests of intestinal function might help differentiate these conditions and improve symptom management.

REFERENCES

1. Bassotti G, Bellini M, Pucciani F, et al. An extended assessment of bowel habits in general population. *World J Gastroenterol* 2004; 10:713-716.
2. Drossman DA, Li Z, Andruzzi E, et al. Householder survey of functional gastrointestinal disorders. Prevalence, sociodemography and health impact. *Dig Dis Sci* 1993;38:1569-1580.
3. Thompson WG, Longstreth GF, Drossman DA, Heaton K, Irvine EJ, Mueller-Lissner S. Functional Bowel disorders and functional abdominal pain. In: Drossman DA Corazziari E, Talley NJ, Thompson WG, Whitehead WE editors. Rome II: the functional gastrointestinal disorders. McLean, VA: Degnon Associates; 2000, p.351-432.
4. Pare P, Ferrazzi S, Thompson WG, et al. An epidemiological survey of constipation in Canada: definition, rates, demographics, and predictors of health care seeking. *Am J Gastroenterol* 2001;96:3130-3137.
5. Whitehead WE, Wald A, Diamant NE, Enck P, Pemberton, JH, Rao SSC. Functional disorders of the anus and the rectum. In: Drossman DA Corazziari E, Talley NJ, Thompson WG, Whitehead WE editors. Rome II: the functional gastrointestinal disorders. McLean, VA: Degnon Associates; 2000, p.483-532.
6. Whitehead WE. Patient subgroup in IBS that can be defined by symptom evaluation and physical examination. *Am J Med* 1999; 107(5A):33S-40S.
7. Mertz H, Naliboff B, Mayer EA. Symptoms and physiology in severe chronic constipation. *Am J Gastroenterol* 1999;94:131-138.
8. Corazziari E, Bausano G, Torsoli A, et al. Italian cooperative study on chronic constipation. In: Wienbeck M. Ed. *Motility of the Digestive tract*. New York, Raven Press, 1982: pp 523-526.

CONSTIPATION IN PATIENTS WITH UPPER GASTROINTESTINAL DISORDERS

N PALLOTTA

Department of Clinical Sciences, University "La Sapienza", Rome, Italy

In the absence of any objective marker, i.e. presence of organic and/or physiological abnormalities, Functional Gastrointestinal Disorders (FGIDs) rely for their definition on symptoms alone. Although, based on five anatomical regions patients with FGIDs have been classified in five subgroups, overlap of symptoms between different FGIDs often occurs and a clear separation between common disorders such as dyspepsia, functional constipation and oesophageal disorders may not be possible. Furthermore since symptoms may wax and wane and may change overtime a number of patients may be classified in a specific subgroup depending on the presenting symptoms in a given period.

The objective of this talk is to review the relationship between constipation and upper GI disorders, specifically functional dyspepsia (FD) and gastro-oesophageal reflux disease (GERD). In examining this issue we focus on:

1. epidemiology
2. underlying pathophysiology
3. management of patients.

Epidemiology

In the assessment of the prevalence of the overlap between constipation, FD and GERD we have to keep in mind that:

1. it may be difficult to separate patients with functional constipation from those with constipation predominant IBS and those with pelvic floor dyssynergia;
2. functional dyspepsia is a vanishing syndrome and a number of studies failed to demonstrate the value, if any, to classify patients in subgroups based on either symptom cluster or predominant symptom. Furthermore the diagnosis of FD is based on upper GI endoscopy and is often difficult to separate FD from non-erosive gastro-oesophageal reflux disease presenting with epigastric pain only;
3. there is a lack of prospective studies confirming the validity of the symptoms grouping since the recall bias may affect substantially the identification of these symptoms. Talley et al¹ in a random sample of Sidney residents in Penrith, by means of mailed self-report questionnaire, showed that 60%

Lectures

of the population reported four or more GI symptoms. The assessment of symptoms profile identified by the factor analysis, showed that these may overlap or may be differentiated in four symptom grouping based on the Rome criteria. The group of healthy subjects provided a clear contrast with all 3 other groups, exhibiting low factor scores on all factors. The dyspepsia group was differentiated by a major presentation of dyspeptic symptoms and some presentation of passing rectal mucus, but low scores on constipation suggesting that upper and lower functional GI disorders are separate conditions in the general population. More recently² by means of self-reported questionnaire mailed to a random sample of Olmsted County residents, the prevalence rate of different combinations of GI symptom complexes was estimated. People with GERD, dyspepsia, IBS, constipation and diarrhoea were identified according to standard definitions. Each of the two and three symptom combination was present in at least 1% of the population. The prevalence rate ranged from 8.4% for the combination of diarrhoea/reflux to 1.3% for the combination of constipation/diarrhoea/dyspepsia. Combination of constipation/reflux was reported by 5.7% of subjects, dyspepsia/constipation by 3.9%, dyspepsia/constipation/reflux by 2.4%. These data suggest a common pathophysiology for GI symptoms and raises the question of whether FGIDs should be considered multiple separate disorders or a single clinical entity. In patients with functional dyspepsia referred to a tertiary centre in Italy, in whom the diagnosis of IBS was excluded, symptoms of bowel disorder were reported by 29% of the patients; 22% matching the Rome II diagnostic criteria for functional constipation and 7% for unspecified functional bowel disorders.

Pathophysiology

An unresolved key issue in the epidemiology of GI symptoms is why there is a striking overlap of chronic upper and lower complaints. One of the explanation for the observed overlap is that the different functional GI disorders may have a similar underlying etiopathogenesis and/or that various FGIDs represent various aspects of the spectrum of a single disorder, and are based therefore on a common pathophysiology. Similarities in demographics and proposed pathophysiological mechanism would support this argument. Patients with FGIDs are typically younger, female and resident in developed rather than developing environment, and dysmotility, visceral hypersensitivity, disordered cerebral perception, psychopathology and subtle inflammation have all been variably invoked in the etiology of all functional disorders.

Delayed gastric emptying has been associated with a variety of FGIDs. In functional dyspepsia³ it has been implicated in the pathogenesis of the syndrome while in others such as GERD, IBS and functional constipation delayed gastric emptying has been invoked to explain the occurrence of dyspeptic symptoms in disorders affecting a different organ. Although a univocal relationship between disordered gastric motor function and occurrence of symptoms has not been found, the high prevalence of gastric motor dysfunction may indeed offer an explanation for the clinical overlap of the various FGIDs.

A recto-gastric inhibitory reflex has been hypothesized as a possible link between constipation, GERD, and dyspepsia. Colonic distension induces fundic relaxation and in human volunteers in-

hibition of defecation⁴ and rectal distension⁵ delay gastric emptying. All of the above observations identify a neural circuitry and provide a physiologic basis for gastric dysfunction and, thereby foregut symptoms in functional constipation. Patients with slow transit constipation frequently have delayed gastric emptying⁶⁻⁸ and have complaints related to the upper GI tract. However the effect of faecal stasis in the large bowel on gastric emptying appears to be determined by the type of constipation according to the large bowel segment through which the transit is prolonged. Delayed gastric emptying occurs in patients with slow transit in the right or left colon but not in those with slow transit in the recto-sigmoid^{6,9-10}. Furthermore subtotal colectomy with ileo-rectal anastomosis has no effect on delayed gastric emptying in patients with idiopathic slow transit constipation characterized by stasis in the transverse colon¹¹. The activation of the colo-gastric reflex could contribute to delayed gastric emptying in this context. Another possibility is that delayed gastric emptying in constipation may indicate a motor disorder involving the entire GI tract. This is a critical issue in patients being considered for colectomy for severe, intractable slow-transit constipation. However, the precise significance of these findings and the relationship between an altered gastric emptying and symptoms in patients with functional constipation remains unclear. Furthermore the observation that some, but not all, such patients show normalized gastric emptying during long-term follow-up after colectomy⁸ suggests that the pathophysiology of delayed gastric emptying is complex and deserves further studies in this patient population.

Management of patients

The relationship between delayed gastric emptying and occurrence of upper GI symptoms is far to be clarified. Several studies failed to demonstrate a univocal relationship between improvement of gastric emptying and symptom remission. We have recently shown that in patients with functional dyspepsia only nausea and none of the other GI symptoms were significantly associated with delayed gastric emptying¹². These findings raise the question whether we should attempt to normalize gastric emptying in patients with slow transit constipation. The observation⁹ that bowel cleansing improved gastric emptying in about 70% of patients with prolonged gastrointestinal transit time and delayed gastric emptying, suggests to treat constipation in order to ameliorate dyspeptic symptoms in this patients population. It can be hypothesized that treatment of constipation, improving gastric emptying may be useful also in those patients with GERD and constipation who do not respond satisfactorily to a standard dose of IPP.

REFERENCES

1. Talley NJ, Boyce P, Jones M. Identification of distinct upper and lower gastrointestinal symptom groupings in an urban population. *Gut* 1998;42:690-695.
2. Locke II GR, Zinsmeister AR, Fett SL, et al. Overlap of gastrointestinal symptom complexes in a US community. *Neurogastroenterol Motil* 2005;17:29-34.
3. Quigley EMM. Review article: gastric emptying in functional gas-

- trointestinal disorders. *Aliment Pharmacol Ther* 2004;20:56-60.
4. Tjeerdma HC, Smout AJ, Akkermans LM. Voluntary suppression of defecation delays gastric emptying. *Dig Dis Sci* 1993;38:832-6.
 5. Coremans G, Geypens B, Vos R, et al. Influence of continuous isobaric rectal distension on gastric emptying and small bowel transit in young healthy women. *Neurogastroenterol Motil* 2004;16:107-11.
 6. Van der Sijp JR, Kamm MA, Nightingale TM, et al. Disturbed gastric and small bowel transit in severe idiopathic constipation. *Dig Dis Sci* 1993;38:837-44.
 7. Mollen RM, Hopman WP, Kuijpers HH, Jansen JB. Abnormalities of upper gut motility in patients with slow-transit constipation. *Eur J Gastroenterol Hepatol* 1999;11:701-8.
 8. Hemingway DM, Finlay IG. Effect of colectomy on gastric emptying in idiopathic slow-transit constipation. *Br J Surg* 2000;87:1193-6.
 9. Badiali D, Pallotta N, Habib FI, Frandina C, Anzini F, Corazziari E. Gastric-emptying is delayed in slow colonic transit constipation. *Gastroenterology* 1998;A715.
 10. MacDonald A, Baxter JN, Bessent RG, et al. Gastric emptying in patients with constipation following childbirth and due to idiopathic slow transit. *Br J Surg* 1997;84:1141-3.
 11. Mollen RM, Hopman WP, Oyen WJ, et al. Effect of subtotal colectomy in gastric emptying of a solid meal on slow-transit constipation. *Dis Colon Rectum* 2001;44:1189-95.
 12. Pallotta N, Pezzotti P, Calabrese E, et al. Relationship between gastrointestinal and extra-gastrointestinal symptoms and delayed gastric emptying in functional dyspeptic patients. *World J Gastroenterol* 2005;11:4375-4381.

PHARMACOLOGICAL TREATMENT OF CONSTIPATION

S MUELLER-LISSNER

Humboldt University, Department of Internal Medicine
Park-Klinik Weissensee, Berlin, Germany

The prevalence of constipation increases with age, and women are more likely to report constipation than men. This is particularly relevant when considering the additional risk of constipation in pregnant women in whom the prevalence of constipation is quite high and when considering that chronic constipation requires long-term treatment.

Although evidence suggests that high-fibre diets and psyllium-containing bulk-forming laxatives may help relieve constipation they are far from being effective in all patients. In addition, fibre supplements may actually exacerbate symptoms associated with constipation, such as abdominal bloatedness and cramping. Hence a diet rich in fibre should be tried but the success rate should not be expected to be very high.

Osmotic laxatives are a heterogeneous group comprising macrogol (polyethylene glycol = PEG), sugars (e.g. lactulose), sugar alcohols (e.g. sorbitol) and saline osmotics (e.g. magnesium hydroxide). Osmotic laxatives oppose the dehydration of bowel contents and hydrate the bowel contents, leading to modification of stool consistency and increased faecal bulk. The increased retention of water in the colon lubricates and softens stools, and allows comfortable bowel action. Polyethylene glycol and saline laxatives pass virtually unchanged through the whole gastrointestinal tract, including the colon. They are not metabolized by the colonic microflora. Macrogol is superior to lactulose in terms of efficacy and tolerability since lactulose is split by the colonic microflora hence losing its osmotic property and since large amounts of gas may arise. Saline laxatives do not taste well, and small amounts may be absorbed which may become a problem in heart and renal failure. The anthraquinones (sennosides) and dimethylmethane derivatives (bisacodyl and sodium picosulfate) have a dual action. They decrease water absorption from the colon or may even induce secretion, and they directly stimulate propulsive colonic motility. The currently used preparations are activated or released in the colon. Stimulant laxatives have a fast onset of action, and these treatments are usually taken at night to produce a morning bowel action. Both the short-term and long-term use of these substances are safe as long as recommended doses are used. Abdominal cramps sometimes accompany their use. It is unlikely that stimulant laxatives at recommended doses are harmful to the colon. Melanosis coli is an easily visible brown discoloration of the colon which may occur within weeks to months of regular use and disappears after stopping intake. There is no indication of a functional relevance. The belief that chronic use of stimulant laxatives damages the colonic myenteric system is largely derived from uncontrolled observations in humans and from conflicting data obtained in prospective studies of animals. It is difficult to understand whether the abnormalities observed in resected colons of constipated patients are a consequence of excessive laxative intake or whether they represent pre-existing changes of unknown aetiology which lead to a functional impairment (disordered ab-

Lectures

sorption or motility). When analysing the respective literature it is unlikely that stimulant laxatives at recommended doses are harmful to the colon. A proportion of patients with chronic constipation is dependent of laxatives to achieve satisfactory bowel function, but this is not the result of prior laxative intake. Tolerance to stimulant laxatives seems to be uncommon in the majority of users. There is no indication for the occurrence of “rebound constipation” after stopping laxative intake. While laxatives may be misused there is no potential for addiction.

The so-called colokinetics belong to the class of 5-HT₄ agonists. The first to be developed was cisapride which has been withdrawn from the market because of potential drug interactions. Prucalopride was very effective but has not been marketed because of safety concerns. The only compound available from this group is the partial serotonin agonist, tegaserod. It has been shown in large controlled trials to be effective in chronic constipation and constipation-predominant irritable bowel syndrome. Apparently, it does not have side effects.

Beyond general safety requirements for drugs, pregnancy and lactation pose particular concerns. For sennosides there are no clinical reports regarding teratogenicity, the respective animal studies were negative. The same holds true for abortion. Excretion in breast milk is minor for senna (< 0.1 % of dose). Three to four percent of the active metabolite of bisacodyl, BHPM, are excreted in urine showing that the drug is absorbed to a minor extent. Data on excretion in breast milk could not be found. Only minor absorption of macrogol (PEG) is likely, but there are no data published. Tegaserod is excreted in breast milk to a high degree (experiments in rats); there is no published experience in humans regarding pregnancy and lactation. Salinic laxatives and sugars should be innocent, and there is no indication of a harmful effect in pregnant and lactating women. In summary therefore, there is no basis to warn against the moderate use of laxatives during pregnancy when constipation poses a problem.

REFERENCES

1. Kamm MA, Mueller-Lissner S, Talley NJ, et al. Tegaserod for the treatment of chronic constipation: a randomized, double-blind, placebo-controlled multinational study. *Am J Gastroenterol* 2005; 100: 362-372.
2. Mueller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and misconceptions about chronic constipation. *Amer J Gastroenterol* 2005; 100: 232-42.
3. Thompson WG, Longstreth GE, Drossman DA, Heaton KW, Irvine EJ, Mueller-Lissner SA. Functional bowel disorders and functional abdominal pain. *Gut* 1999; 45 (Suppl II): II43-II47.
4. Tytgat GN, Heading RC, Muller-Lissner S, et al. Contemporary understanding and management of reflux and constipation in the general population and pregnancy: a consensus meeting. *Aliment Pharmacol Ther* 2003; 18: 291-301.
5. *Pharmacology* 1993, 47 (suppl 1): 146-54.

NON-PHARMACOLOGICAL TREATMENT OF CONSTIPATION

DF ALTOMARE

Department of Emergency and Organ Transplantation, General Surgery and Liver Transplantation Unit, University of Bari, Bari, Italy

The fine neurological mechanism controlling colonic functions (absorption, secretion, immune response and motility) and defecation is highly complex as it involves the ENS, autonomic system and CNS, with various possible points of interaction between these and the environment. For this reason, any dysfunction within this complex inter-relationship can lead to some form of colonic malfunction, the most common being constipation.

Functional constipation can be broadly divided into slow transit constipation and obstructed defecation, although they may occur simultaneously. Both conditions may be suitable for non-pharmacological treatment if traditional therapy fails.

BIOFEEDBACK TRAINING has been used in patients with obstructed defecation due to pelvic floor dyssynergia and, less frequently, in those with slow transit constipation. The results in the latter indication are usually disappointing because of the poor rationale underlying its application¹ and, although meta-analyses have shown success rates of 69-78%, its role in obstructed defecation is controversial.² Most of the published studies are unreliable and their results are difficult to compare because of the use of different therapeutic protocols, different patient indications and different evaluation criteria. Furthermore, it is generally believed that the long-term results deteriorate over time³.

SACRAL NERVE MODULATION (SNM) is a new therapy that was originally indicated for the treatment of urinary and faecal incontinence. At first, an electrode is percutaneously implanted in the sacral nerves through the S3 foramen and temporarily connected to an external electrostimulator in order to test therapeutic efficacy for at least two weeks (PNE test), and then the patients who respond favourably are switched to permanent SNM via a totally implantable pulse generator connected to the sacral electrode. A number of clinical observations have confirmed that the technique also has some beneficial effects on constipation. There are only two published papers describing the effect of SNM on constipation, and these involved very small case series^{4,5}; however, the Italian Group for Neurostimulation (GINS) has recently presented the outcome of 37 patients (16 with slow transit constipation) who experienced a substantial improvement after the PNE test and subsequently underwent permanent implantation.

SURGERY for SLOW TRANSIT CONSTIPATION is the last resort in highly selected cases unresponsive to any other treatment. Total colectomy was advocated by Sir Arbuthnot Lane in the late XIX century,⁶ but was then abandoned until interest was revived in the final decades of the last century; however, the results were inconsistent probably because of inappropriate patient selection (irritable bowel syndrome, obstructed defecation, systemic autonomic neuropathy). The most recent experiences are more re-

assuring and have led to high success rates^{7,8}. Total colectomy with ileorectal anastomosis is usually preferred to subtotal colectomy, which may lead to small bowel obstruction (in up to 25% of cases), persisting abdominal symptoms (15%) or diarrhoea (10%)⁹. Careful patient selection is crucial, and must exclude patients with IBS, concurrent obstructed defecation and autonomic disease involving the ileum, stomach or gallbladder.

The use of subtotal colectomy with ceco-rectal anastomosis has recently been suggested¹⁰ as a means of overcoming the problem of bacterial overgrowth in the ileum and preserving water and electrolyte absorption in the caecum.

However, the most challenging condition is severe constipation associated with faecal incontinence, as in the case of patients with myelodegenerative diseases, spinal trauma or pan-enteric autonomic neuropathy. This selected group of patients could be offered the Malone antegrade colonic enema (ACE), one of the best technical variations of which is the Marsh and Kiff ileocaecostomy,¹¹ which has been further modified by our group. In this procedure, the ileostomy is created using the terminal ileum, which is narrowed by means of a linear stapler to establish the Mitrovannoff principle while leaving the ileocaecal valve inside; the remaining ileum is anastomosed to the ascending colon and intussuscepted in order to create a nipple valve to prevent caeco-ileal reflux.

Terminal ileostomy or colostomy may be a last resource for treating this disabling condition in the case that other techniques fail.

Surgery for obstructed defecation

Obstructed defecation may be due to dysfunctional problems (rectal inertia, anismus) and/or anatomical alterations of the anorectum (rectocele, intussusception, perineal descent).

Functional obstructed defecation can be treated by means of biofeedback or a botulin toxin A sphincter injection,¹² thus allowing the patient to relax the puborectalis muscle appropriately during defecation.

The treatment of rectocele and intussusception is still debated. Abdominal rectopexy has led to disappointing results in the treatment of rectal intussusception¹³. A new transanal technique involving the resection of the distal part of the rectum by two circular stapler devices (the STARR technique) has recently been proposed,¹⁴ but the lack of clear indications and information concerning the long-term results has aroused some perplexity, especially as the technique has been blamed for causing some rare but severe complications¹⁵. Rectocele can be repaired using trans-anal, trans-vaginal, trans-perineal and trans-abdominal techniques.

However, there is still considerable debate among colorectal surgeons about the best technique for the treatment of all the above disorders as very new technique seems to work miracles for a while, but the results of subsequent routine clinical experience always seem to be much more disappointing.

REFERENCES

1. Chiarioni G, Salandini L, Whitehead WE. Biofeedback benefits only patients with outlet dysfunction, not patients with isolated slow transit constipation. *Gastroenterology* 2005;129:86-97.
2. Heymen S, Jones KR, Scarlett Y, Whitehead WE. Biofeedback treatment of constipation: a critical review. *Dis Colon Rectum* 2003;46:1208-17.
3. Battaglia E, Serra AM, Buonafede G, et al. Long-term study on the effects of visual biofeedback and muscle training as a therapeutic modality in pelvic floor dyssynergia and slow-transit constipation. *Dis Colon Rectum* 2004;47:90-95.
4. Kenefick NJ, Nicholls RJ, Cohen RG, Kamm MA. Permanent sacral nerve stimulation for treatment of idiopathic constipation. *Br J Surg* 2002;89:882-8.
5. Malouf AJ, Wiesel PH, Nicholls T, Nicholls RJ, Kamm MA. Short-term effects of sacral nerve stimulation for idiopathic slow transit constipation. *World J Surg* 2002;26:166-70.
6. Lane WA. The results of operative treatment of chronic constipation. *Br Med J* 1908;1:1125-1128.
7. Pluta H, Bowes KL, Jewell LD. Long-term results of total abdominal colectomy for chronic idiopathic constipation. Value of preoperative assessment. *Dis Colon Rectum* 1996;39:160-6.
8. Aldulaymi BH, Rasmussen OO, Christiansen J. Long-term results of subtotal colectomy for severe slow-transit constipation in patients with normal rectal function. *Colorectal Dis* 2001;3:392-5.
9. Knowles CH, Scott M, Lunniss PJ. Outcome of colectomy for slow transit constipation. *Ann Surg* 1999;230:627-38.
10. Sarli L, Iusco D, Violi V, Roncoroni L. Subtotal colectomy with antiperistaltic cecorectal anastomosis. *Tech Coloproctol* 2002; 6:23-6.
11. Marsh PJ, Kiff ES. Ileocaecostomy: an alternative surgical procedure for antegrade colonic enema. *Br J Surg* 1996;83:507-8.
12. Maria G, Brisinda G, Bentivoglio AR, Albanese A, Sganga G, Castagneto M. Anterior rectocele due to obstructed defecation relieved by botulinum toxin. *Surgery* 2001;129:524-9.
13. Orrom WJ, Bartolo DC, Miller R, Mortensen NJ, Roe AM. Rectopexy is an ineffective treatment for obstructed defecation. *Dis Colon Rectum* 1991;34:41-6.
14. Boccasanta P, Venturi M, Stuto A, et al. Stapled transanal rectal resection for outlet obstruction: a prospective, multicenter trial. *Dis Colon Rectum* 2004;47:1285-96.
15. Dodi G, Pietroletti R, Milito G, Binda G, Pescatori M. Bleeding, incontinence, pain and constipation after STARR transanal double stapling rectotomy for obstructed defecation. *Tech Coloproctol* 2003; 7:148-53.

Lectures

MANAGEMENT OF CONSTIPATION IN CHILDREN WITH DISORDERS OF INTESTINAL FUNCTION

A STAIANO

Department of Pediatrics, University "Federico II", Naples, Italy

The prevalence of childhood constipation is estimated to range between 0.3-28%. Approximately 3% of general pediatric outpatients visit and 25% of pediatric gastroenterology consultations are related to a defecation disorder. In more than 90% of all age groups no obvious cause can be identified; in fact beyond the neonatal period, the most common cause of constipation is functional and has been called idiopathic constipation.

A careful medical history together with a complete physical examination is all is needed for diagnosis of most children with constipation¹. Important informations include: the time after birth of the first bowel movement; the length of time the condition has been present; stools frequency, consistency and size; the presence of encopresis; an history of retenting posturing; whether defecation is painful, whether blood has been present on the stool or the toilet paper and whether the child experiences abdominal pain. An history of delayed passage of meconium; fever, abdominal distention, anorexia, nausea and vomiting, weight loss or poor weight gain could be a sign of an organic disorder. Finally is essential to assess child's psychosocial history; the family structure, the number of people living in the child's home and their relationship to the child; school problems and the possibility of sexual abuse. Dietary history and the history of previous treatment strategies for constipation should also be determined.

A complete physical and neurological examination should be performed in all children with defecation disorders. External examination of the perineum and perianal area is essential and provides informations about the position of the anus, perianal faeces, redness, dermatitis, eczema, fissures, haemorrhoids and sexual abuse. At least one digital examination of the anorectum is recommended. The anorectal digital examination assesses perianal sensation, anal tone, the size of the rectum, the amount and consistency of stool in the rectum, the voluntary contraction and relaxation of the anal sphincter and the presence of the anal wink.

Consultation with a pediatric gastroenterologist becomes necessary when therapy fails, when there are concerns that an organic disease exists or when management is complex. It is recommended that the primary care physician considers whether the children who require evaluation by a specialist should have blood tests to identify evidence of hypothyroidism, hypercalcemia, coeliac disease and lead toxicity.

An abdominal radiograph is not indicated to establish the presence of faecal impaction if the rectal examination reveals the presence of large amounts of stool. It might only be helpful when there is a doubt about whether a patient is constipated, in a child who is obese or who refuses a rectal examination, or in whom there are psychologic factors such as sexual abuse that make rectal examination inappropriate and traumatic. Some patients have a history of infrequent bowel movements but have no objective findings of constipation. In these patients an evaluation of colonic transit time with radiopaque markers may be helpful. The marker test is useful to differentiate between children with constipation

and children with functional non-retentive faecal soiling (FN-RFS). A normal colonic transit time together with a normal defecation pattern without rectal mass on physical examination confirms the diagnosis of FN-RFS. In these children oral laxative should increase the encopresis frequency while the best treatment is a strict toilet training.

The most common condition in infancy that must be differentiated from functional constipation is Hirschsprung's disease. Rectal biopsy with histopathologic examination and ano-rectal manometry are the only tests that can reliably exclude Hirschsprung's disease. The presence of relaxation of the internal sphincter induced by transient distention of the rectum during anorectal manometry excludes Hirschsprung's disease. However false positive results may be due to technical factors such as insufficient insufflation of the catheter in the sphincter complex. The recto-anal inhibitory reflex may also be absent in children with megarectum. The general approach to the child with functional constipation includes the following steps: 1) education; 2) disimpaction; 3) prevention of reaccumulation of faeces and 4) follow up.

Intensive support, education and reassurance of children and parents in combination with a non-accusatory approach by the physician and parents are crucial at the beginning of medical treatment for defecation problems. Before treatment is started it should be stressed that progress of treatment is often irregular and marked by periods of improvement alternating with periods of deterioration; for this reason the duration of maintenance therapy usually requires 6 to 24 months. A combination of behavioural treatment (toilet training with a rewarding system), cognitive therapy and laxative treatment is very useful to restore normal bowel habits by positive reinforcement. In fact in a large pediatric prospective randomized controlled trial a higher cure rate was found in children receiving behavioural intervention (toilet training, positive reinforcing scheme and dietary advice) plus laxatives compared to those receiving medical intervention alone².

Rectal disimpaction is necessary before initiation of maintenance therapy. Uncontrolled trials have described successful disimpaction by the oral route, the rectal route or the combination of the two. PEG at a dose of 1.5 g/kg/d for 3-4 days has been successfully and safely used for faecal disimpaction in children³. Rectal disimpaction may be performed with phosphate soda enemas, saline enemas, or mineral oil enemas followed by a phosphate enema. The use of soapsuds, tap water, and magnesium enemas is not recommended because of their potential toxicity. Rectal disimpaction has also been effectively performed with glycerine suppositories in infants and bisacodyl suppositories in older children. Once disimpaction has been achieved, it is essential to begin oral daily laxative immediately and continue treatment for months or longer to prevent reaccumulation of stool. The correct dose is that which produces a daily soft stool without side effects. The main function of the osmotic laxatives is to loosen stool consistency, thus facilitating transport and expulsion and rendering defecation less painful. The correct dose is that which produces a daily soft stool without side effects. The adequate dose should be continued for at least 3 months. Two randomised controlled trials compared lactilol and lactulose, both disaccharides derived from lactulose. They were both equally effective in increasing defecation frequency and normalizing stool consistency. More recently poly-

ethylene glycols (PEGs) have been suggested as alternative laxatives in adults and children with constipation. One study comparing PEG to lactulose in children reported an equal effect on stool frequency, consistency and straining in both groups. Parents rated the improvement of their child higher while receiving PEG compared to lactulose as 87% vs 46%⁴. Side effects were mild in all pediatric patients studied. A recent study shows that a three day course of PEG 3350 was safe and effective in the treatment of childhood faecal impaction at doses between 1 and 1.5 g/kg/d. In children one double blind randomised controlled trial has been performed showing that PEG and lactulose both significantly increase defecation frequency and decrease encopresis frequency⁵. Success was more present in the PEG group (56% vs 29%) after 8 weeks. Abdominal pain, straining, and pain on defecation were reported significantly less.

There is evidence that PEG is of value in the treatment of constipation in children, however more randomized controlled trials are needed to confirm this observation.

REFERENCES

1. Backer SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: Evaluation and Treatment. *J Pediatr Gastroenterol Nutr* 1999;29:612-626.
2. Pashankar DS, Uc A, Bishop WP. Polyethylene glycol 3350 without electrolytes a new safe, effective, and palatable bowel preparation for colonoscopy in children. *J Pediatr* 2004;144:358-62.
3. Borowitz S, Cox DJ, Sutphen JL, et al. Treatment of childhood encopresis: a randomized trial comparing three treatment protocols. *J Pediatr Gastroenterol Nutr* 2002;34:378-84.
4. Gremse DA, Hixon J, Crutchfield A. Comparison of polyethylene glycol 3350 and lactulose for treatment of chronic constipation in children. *Clin Pediatr (Phila)* 2002;41:225-9.
5. Voskuijl W, de Lorig F, Verwijs W, et al. PEG 3350 (Transipeg) versus lactulose in the treatment of childhood functional constipation: a double blind, randomized, controlled, multicenter trial. *Gut* 2004; 53:1590-4.

THE SIGNIFICANCE OF THE PLACEBO RESPONSE IN FUNCTIONAL GASTROINTESTINAL DISORDERS

W GRANT THOMPSON

University of Ottawa, Canada

Until the middle of the twentieth century, a placebo was defined as a treatment or pill given more to please than cure the patient. Especially for minor, self limited complaints, physicians prescribed sugar pills implying that they might help. The randomized, controlled clinical trial originated in the 1930s, and inert treatments used as controls became known as “placebos”. New graduates use the term in the latter sense. This is the pity, because while the surreptitious use of inert treatments is unethical, the *placebo effect* is an important component of all treatment and should be exploited.

In a randomized, placebo-controlled clinical trial, an outcome (treatment benefit) is estimated for a group of subjects receiving the test treatment and a similar group receiving a placebo such as a pill that is apparently identical to the test treatment. In a positive study, the difference in outcomes between these two groups is known as the *therapeutic gain*, which if statistically significant proves the drug has a benefit. This process is the essence of *evidence-based medicine*. However in all clinical trials, especially those of treatments for chronic diseases such as the functional gastrointestinal disorders (FGID), those receiving the placebo will improve as well. There are several reasons for this *placebo response*, but the principle two are the natural tendency for chronic disorders to improve without treatment and the *placebo effect*. In most clinical trials of treatments for FGID, the placebo response is 50% or more, far greater than the improvement due to the therapeutic gain. It is important to understand that the factors underlying the placebo response (natural history and placebo effect) are at work in both treatment arms. Thus the “therapeutic equation”:
Treatment benefit = Therapeutic gain + natural history of the disease being treated + the placebo effect.

In an individual, it is impossible to identify which of these three components is important – one, two, or all three. However, in clinical trials where large numbers of people are included, a therapeutic gain may be identified. When treatment is stopped, the number of improved patients falls – but seldom to zero. In the placebo group that fall may represent the loss of the placebo effect, while in the treatment group the fall represents the loss of both the placebo effect and the therapeutic gain. The number of improved subjects post treatment may indicate the result if no treatment had been given; that is the disorder’s “natural history”. This simplistic concept illustrates the interactions of these components in any treatment.

Of course, the natural history will depend upon the circumstances of the trial and disease being treated. It will be very different in cancer (downhill), hypertension (stable), or chronic conditions (fluctuating). The FGID and other chronic painful conditions such as joint pains, headaches and backache typically fluctuate. Healers know this instinctively, and often rely on the passage of time to heal, rather than introduce useless or potentially harmful treatments. A mentor once termed this “masterful inactivity”.

Our subject here is the *placebo effect*, and it is important to consider how that might be maximized as we deliver treatment, be-

Lectures

cause the careful and compassionate generation of a placebo effect with legitimate treatments is not only important but ethical. A placebo effect may be augmented by relief of anxiety, conditioning through previous encounters with healers, personal and societal expectations, the delivery of a satisfying diagnosis or meaning for symptoms and the authority, personality and compassion of the healer. Often termed the “art of medicine”, exploitation of the placebo effect dominated the history of healing, and along with the body’s natural struggle to recover explains the centuries-long employment of even harmful remedies such as blood-letting and purging, and the popularity of most contemporary non-scientific remedies such as homeopathy and acupuncture.

Just as the placebo effect may make patients feel better, so clinical interactions that promote anxiety, negative conditioning, disappointed expectations, or insufficient authority, care and compassion can have *nocebo effects*. Consider:

Treatment benefit = Therapeutic gain + natural history of the disease being treated - the nocebo effect.

It is apparent that a large nocebo effect could overwhelm any therapeutic gain making a patient feel worse. Nocebo effects account for much patient dissatisfaction and malpractice litigation.

It is a great irony that our grandparents’ doctors with few scientific cures were loved and honored because of their compassion and other non-scientific skills, while modern physicians who may often heal with science but permit little time for these skills, are unloved and criticized. Nowhere is this more apparent than in the FGIDs. Science can do much to be sure. It permits us to probe, visualize and measure the entire gut and thereby exclude structural disease. Some drugs may palliate, but science does little to cure the functional gut disorders. Exploitation of time’s healing effect and the placebo effect will remain the principle therapy for FGIDs for the foreseeable future. Restoration of a therapeutic relationship through compassionate doctor/patient relationships should be an important therapeutic objective for all who care for such patients.

REFERENCES

1. Thompson WG. *The Placebo Effect in Health: combining science and compassionate care*. New York: Prometheus, 2005.
2. Harrington A. Introduction. In: Anne Harrington, editor. *The Placebo effect*. Cambridge, Mass: Harvard, 1997:1-11.
3. Hahn RA. The Nocebo Phenomenon, Scope and Foundations. In: Harrington A, editor. *The Placebo Effect*. Cambridge, Mass., London: Harvard University Press, 1997:56-76.
4. Shapiro AK, Shapiro E. *The Powerful Placebo: From Ancient Priest to Modern Physician*. Baltimore: Johns Hopkins Press, 1997.
5. Thompson WG. Placebos: a review of the placebo response. *Am J Gastroenterol* 2000;95:1637-1643.

SEROTONERGIC DRUGS FOR THE TREATMENT OF DISORDERS OF INTESTINAL FUNCTION

M TONINI

Department of Physiological and Pharmacological Sciences, University of Pavia, Pavia, Italy

In the gut, serotonin (5-hydroxytryptamine: 5-HT) acts as a paracrine signalling molecule released by enterochromaffin cells and as a transmitter released by some descending serotonergic interneurons. It has a prominent role in the regulation of motility, vascular tone, secretion and perception both in normal and under certain pathophysiological conditions, such as the carcinoid syndrome and the irritable bowel syndrome (IBS). The evidence that several factors involved in the control of 5-HT (production/release/re-uptake mechanisms) are changed in these syndromes has led to the idea that they are partly based on a dysregulation of 5-HT function¹.

Serotonin is known to markedly influence bowel function by activating at least five receptor types (5-HT_{1,2,3,4,7}). Among all 5-HT receptors, those belonging to the 5-HT₃ (a ionotropic receptor) and 5-HT₄ (a metabotropic receptor) type are the most extensively studied in gastroenterology, resulting in commercially available (although not worldwide) serotonergic agents for the treatment of IBS and functional dyspepsia². The 5-HT₃ receptor antagonist, alosetron, is known to blunt visceral perception, enhance colonic compliance, and reduce postprandial colonic motor response, fluid secretion, and colonic transit. Alosetron is the only drug commercially available in the US market for the treatment of women with severe, diarrhoea-predominant IBS (D-IBS) refractory to conventional therapy. This drug was initially marketed in the USA in February 2000, but was withdrawn in November of the same year because of complications from severe constipation, as well as ischaemic colitis (event rate: 6.7 cases per 1000 person-years of exposure)^{3,4}. On April 2002, the FDA recommended the access to alosetron to be restored through a restricted distribution and use programme. On June 2002, the FDA announced the approval of a supplemental New Drug Application permitting marketing of alosetron with restrictions. Another 5-HT₃ antagonist, cilansetron, has now been tested in patients with diarrhoea-predominant IBS. From results of phase III studies, it appears that this drug is significantly more effective than placebo in both men and women in relieving overall, as well as individual symptoms, including abdominal pain, diarrhoea, frequency and urgency⁴.

To date, a still unanswered question is whether ischaemic colitis is a class effect of the 5-HT₃ antagonists. This fact is complicated by the evidence that in patients with IBS a higher prevalence of ischaemic colitis (from two- to fourfold) has been observed compared to controls. However, the prevalence of ischaemic colitis in patients treated with alosetron was superior to that observed in the general population of IBS patients, thus suggesting a direct involvement of the drug. For cilansetron, the event rate for suspected ischaemic colitis in patients treated with the drug was 3.77 per 1000 person-years of exposure. All of the cases of drug-induced ischaemic colitis resolved without serious sequelae⁴. As for alosetron, the most commonly reported side-effect of

cilansetron was constipation, ranging from 19-40% for the various doses of the drug. Recently, it has been suggested that compounds with partial antagonistic properties at the 5-HT₃ receptor may be safer than pure 5-HT₃ antagonists in D-IBS¹.

As far as 5-HT₄ receptor agonists is concerned, this class of drugs is referred to as gastrointestinal prokinetic agents. Second generation 5-HT₄ partial agonists, such as tegaserod and mosapride, are devoid of the proarrhythmic properties of cisapride. Tegaserod, which is commercially available in a number of non-European Union countries for the treatment of IBS, received FDA approval in July 2002. Evidence from clinical trials indicates that the drug is effective only in female patients with C-IBS². In these patients, tegaserod accelerates oro-caecal and colonic transit and relieves key symptoms including pain and bloating, with a sustained effect over at least one to three months and on re-treatment. Side effects of tegaserod are generally mild, with brief episodes of diarrhoea involving about 10% of patients. Men do not seem to benefit from tegaserod. The reasons for these gender-related responses are currently not known. Based on results of preclinical and clinical studies, it has recently been suggested that the prokinetic effect of tegaserod may depend on the partial 5-HT₄ antagonist properties of the molecule¹. Mosapride is a prokinetic agent of the upper gastrointestinal tract which is marketed in some Asian countries for the treatment of functional dyspepsia.

With regard to fundus-relaxant drugs, sumatriptan, a 5-HT_{1B/D} agonist, has been shown to relax the proximal stomach and to reduce sensitivity to mechanical distension in healthy volunteers, and to improve symptoms of early satiety in patients with functional dyspepsia. Buspirone, a partial 5-HT_{1A} agonist used to prevent panic attacks, was superior to placebo in alleviating symptoms in dyspeptic patients possibly via an enhancement of the accommodation to a meal.

Recently, 5-HT₇ receptors activated by endogenous 5-HT have been found to participate in the accommodation process of the circular muscle during the preparatory phase of peristalsis⁵. Since an exaggerated accommodation of the gut wall may contribute to abdominal distension and bloating, symptoms that accompany many disorders of intestinal function, the 5-HT₇ receptor may emerge as a reliable target for the development of novel therapeutic approaches in gastroenterology.

REFERENCES

1. Tonini M. 5-Hydroxytryptamine effects in the gut: the 3, 4 and 7 receptors. *Neurogastroenterol Motil* 2005;17:637-642.
2. De Ponti F, Tonini M. Irritable bowel syndrome: new agents targeting serotonin receptor subtypes. *Drugs* 2001;61:317-332.
3. Friedel D, Thomas R, Fisher RS. Ischemic colitis during treatment with alosetron. *Gastroenterology* 2001;120:557-560.
4. Chey WD, Cash BD. Cilansetron: a new serotonergic agent for the irritable bowel syndrome with diarrhoea. *Expert Opin Investig Drugs* 2005;14:185-193.
5. Tonini M, Vicini R, Cervio E, et al. 5-HT₇ receptors modulate peristalsis and accommodation in the guinea pig ileum. *Gastroenterology* 2005;129:1557-1566.

TACHYKININ RECEPTOR BLOCKADE AND GASTROINTESTINAL FUNCTION: WHICH ANTAGONISM SHOULD BE PREFERRED TO TREAT DISORDERS OF INTESTINAL FUNCTION?

F DE PONTI

Department of Pharmacology, University of Bologna, Bologna, Italy

The biological effects of endogenous tachykinins in the gut are mediated by tachykinin NK₁, NK₂ and NK₃ receptors, which have respective preferential affinity for SP, NKA and NKB^{1,2}. Their pharmacological characterisation was made possible by the development of potent and selective peptide-derived agonists, and peptide or non-peptide antagonists³⁻⁷ (Table 1).

TABLE 1 - Pharmacology of tachykinin receptor antagonists

Type of antagonist (examples)	Distribution of receptors	Pharmacological action in animals	Pharmacological action in humans
NK ₁ receptor antagonists (e.g. aprepitant, vofopitant, ezlopitant)	Enteric neurons, Cajal interstitial cells, smooth muscle cells, immune cells	Inhibition of motility, vagal afferent sensation, and inflammation	Anti-emetic effects
NK ₂ receptor antagonists (e.g. nepadutant, saredutant)	Enteric neurons, smooth muscle, extrinsic afferents	Inhibition of motility, sensation, and inflammation	Inhibitory effect on NKA-induced motility
NK ₃ receptor antagonists (e.g. osanetant, talnetant)	Enteric neurons, extrinsic afferents	Inhibition of motility and sensation	??

NK₁ receptor antagonists

The NK₁ receptor antagonists include aprepitant, vofopitant, ezlopitant and R-673³. Aprepitant is used to relieve delayed chemotherapy-induced emesis, which suggests they significantly inhibit vagal afferents. Their potential application in functional gut disorders comes from their ability to block the preferential target receptors for substance P in myenteric neurons and afferent pathways as NK₁ receptors are expressed by a number of the neuronal and non-neuronal cells involved in gut motility. Tachykinergic transmission to circular muscle may be mediated by NK₁ receptors on both Cajal interstitial cells and smooth muscle cells. NK₁ receptor blockade may also inhibit peristalsis, an effect that is probably mediated by the inhibition of post-junctional NK₁ receptors. However, most of the published studies were carried out in animals, and the clinical relevance of the observations remains to be determined. TAK 637 (a compound whose development was discontinued because of side effects) dose-dependently reduced abdominal contractions in response to colorectal distension in rabbit by antagonising NK₁ receptors mainly in the spinal cord, and reduced colonic transit and defecation in a Mongolian gerbil model of irritable bowel syndrome (IBS). Other selective NK₁ receptor antagonists (e.g. SR-140333 and MEN-10930) inhibit the colonic propulsive activity induced by NK₁ receptor agonists *in vitro*. Preliminary data suggest that IBS patients are less disturbed by

Lectures

rectal balloon distension after treatment with the CJ-11974 NK₁ receptor antagonist. These antagonists may also have other beneficial effects in IBS as they can inhibit bowel inflammation and have an anti-secretory action.

NK₂ receptor antagonists

The NK₂ receptor antagonists include nepadutant, saredutant, SR-144190 and UK-290795³. The presumed mechanism of action of this class of compounds reflects the preferential binding of NKA/B ligands to NK₂ receptors, which are mainly located on sensory neurons; however, it has been found that intravenous NKA also stimulates gastrointestinal motility in unanesthetised dogs.

Experimental models have shown that prototype NK₂ receptor antagonists such as saredutant dose-dependently reduce agonist-induced faecal excretion, and reduce faecal water excretion and abdominal contractions in response to colorectal distension, but no demonstrable effect on colonic transit was found in stressed rats. Nepadutant competitively binds the human NK₂ receptor expressed in CHO cells with high affinity and specificity, and selectively blocks NK₂ receptors in isolated smooth muscle preparations from animal and human tissues. In *in vivo* animal models, MEN 11420 effectively and lastingly blocks the NK₂ receptors expressed in the smooth muscle of the intestinal, genito-urinary and respiratory tracts.

In a randomised double-blind study, Lördal et al⁸ investigated the importance of NK₂ receptors in the regulation of human intestinal motility with the primary aim of evaluating the ability of MEN 11420 to antagonise NKA-stimulated small bowel motility, and the secondary aims of assessing the effects of MEN 11420 on baseline fasting motility and determining the plasma concentrations at which the inhibition of NKA-stimulated gut motility occurred. Their results showed that nepadutant alleviates the intestinal motor responses evoked by NKA infusion. It had no effect on baseline fasting motility, thus indicating that tachykinins are not involved in the physiological regulation of the MMC via NK₂ receptors, but may be important in diseases in which increased motility is a predominant symptom.

NK₃ receptor antagonists

The NK₃ receptor antagonists include osanetant and talnetant³. Their suggested mechanism of action reflects preferential binding to NK₃ receptors, which are mainly located on sensory neurons: e.g. on the spinal terminals of capsaicin-sensitive neurons and within the intrinsic neurons of the spinal cord. The intrathecal NK₃ receptor antagonist SR 142,801 reduced the behavioural response of rats to noxious colorectal distension. It is also possible that NK₃ receptors play a peripheral role in the mechanisms of intestinal nociception as both talnetant (which crosses the rat blood/brain barrier) and SB-235375 (which does not cross the barrier) reduce colonic sensation (abdominal contractions in response to colorectal distension) without altering colonic compliance⁹.

REFERENCES

1. Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part I. Expression, release and motor function. *Pharmacol Ther* 1997;73:173-217.
2. Holzer P, Holzer-Petsche U. Tachykinins in the gut. Part II. Roles in neural excitation, secretion and inflammation. *Pharmacol Ther* 1997;73:219-263.
3. Giardina GA, Gagliardi S, Martinelli M. Antagonists at the neurokinin receptors - recent patent literature. *Drugs* 2003;6:758-772.
4. Tonini M, Spelta V, De Ponti F, et al. Tachykinin-dependent and -independent components of peristalsis in the guinea pig isolated distal colon. *Gastroenterology* 2001;120:938-945.
5. De Ponti F, Crema F, Moro E, Nardelli G, Croci T, Frigo GM. Intestinal motor stimulation by the 5-HT₄ receptor agonist ML10302: differential involvement of tachykininergic pathways in the canine small bowel and colon. *Neurogastroenterol Motil* 2001;13:543-553.
6. Crema F, Moro E, Nardelli G, De Ponti F, Frigo GM, Crema A. Role of tachykininergic and cholinergic pathways in modulating canine gastric tone and compliance *in vivo*. *Pharmacol Res* 2002;45:341-347.
7. Maselli MA, Piepoli AL, Guerra V, et al. Colonic smooth muscle responses in patients with diverticular disease of the colon: effect of the NK₂ receptor antagonist SR48968. *Dig Liv Dis* 2004;36: 348-354.
8. Lördal M, Navalesi G, Theodorsson E, Maggi CA, Hellström PM. A novel tachykinin NK₂ receptor antagonist prevents motility-stimulating effects of neurokinin A in small intestine. *Brit J Pharmacol* 2001;134:215-223.
9. Fioramonti J, Gaultier E, Toulouse M, Sanger GJ, Bueno L. Intestinal anti-nociceptive behaviour of NK₃ receptor antagonism in conscious rats: evidence to support a peripheral mechanism of action. *Neurogastroenterol Motil* 2003;15:363-369.

ROLE OF CCK1 RECEPTORS IN THE CONTROL OF GASTROINTESTINAL MOTOR FUNCTION AND VISCERAL PAIN

L. BUENO

Neurogastroenterology Unit INRA, Toulouse, France

Among many hormones and neuropeptides, cholecystokinin octapeptide (CCK₈) plays a major role in the control of food intake and gut motility. More recently, data have been accumulated to extend its role in the control of anxiety and the transmission of afferent signals to the brain. CCK activates 2 types of receptors previously called A (for Alimentary) and B (for Brain), recently named CCK₁ and CCK₂ respectively.

In animals and humans, intravenous administration of CCK₈ inhibits gastroduodenal motility and gastric emptying, disrupts the intestinal migrating motor complex and stimulates at least distal colonic motility while inhibition or no effect was observed for the proximal colon. The effects on gastrointestinal motility involved afferent vagal fibers. This peripheral control of gastrointestinal motility is also associated with a centrally mediated action since intracerebroventricular administration of CCK₈ triggers the disruption of the fasted motor pattern replaced by a postprandial type of activity¹. In humans, CCK₈ IV infusion decreases the phasic activity of the proximal colon but stimulates that of the distal colon. However CCK₈ decreased colonic tone at both proximal and distal colon². In contrast, other studies, based on the IV infusion of doses producing maximal pancreatic secretion and gallbladder contractions, were unable to affect colonic transit motility and tone³. Experimental studies in animals suggest that the inhibitory effects of CCK₈ on colonic motility of the proximal colon are mediated through the release of nitric oxide. CCK₈ is also involved in a number of upstream inhibitory reflexes. Indeed, CCK₈ was shown to be responsible of the transient relaxation of the lower esophageal sphincter (TLESRs) in response to gastric distension in humans⁴, this effect involving the release of nitric oxide. CCK₈ also plays a role in the inhibition of pyloric motility induced by fatty meal through activation of a vago-vagal reflex⁵.

In addition to its activation of vagal afferent fibers, CCK₈ participates to the central modulation of nociceptive signals from the gut at dorsal horn level. In recent years, it has become evident that the antinociceptive effects of opioidergic pathways are functionally counterbalanced by endogenous cholecystokinin (CCK) receptors⁶.

Interestingly, it seems that stressful situations facilitate the activation of anti-analgesic CCK mechanisms, which in turn modulate opioid-mediated antinociception⁷.

Co-administration of a CCK antagonist along with an opioid is associated with an improved level of antinociception. Indeed, CCK may prevent the inhibition of C-fiber evoked activity resulting from intrathecal mu agonist administration, an effect reversed by a CCK₂ antagonist⁸.

Proglumide, a CCKA antagonist potentiates the antinociceptive effects of acute morphine administration in acute restraint stress and continuous footshock stress. These last data suggest that hyperalgesia promoted by both inflammation and stress, activates an endogenous opioid antinociception that may be potentiated by

CCK antagonists but the respective role of CCK₁ and CCK₂ receptors in this potentiation remains to be determined.

CCK₈ infusion is known for a long time to trigger abdominal pain sensations particularly in patients with functional bowel disorders⁹. More recently, it was shown that in healthy subjects, CCK-OP at 40 ng kg⁻¹ h⁻¹ by IV route produces a significant decrease in sensory thresholds compared with the basal period during rapid phasic distension but not during slow ramp distension¹⁰. This effect is not associated with change in compliance. The fact that CCK-OP decreases sensory thresholds during rapid phasic distension suggests that CCK-OP may preferentially stimulates serosal mechanoreceptors rather than mucosal mechanoreceptors stimulated during slow ramp distensions. Modulation of rectal sensitivity by CCK suggests that this neuropeptide could be implicated in the pathogenesis of the rectal hypersensitivity observed in IBS. Accordingly, CCK₁ receptor antagonists have been tested in the treatment of IBS patients. A large phase II trial has indicated that loxiglumide improves significantly overall symptoms in no diarrhoea IBS group¹¹. A follow-up compound, dexloxiglumide, has been tested in female IBS patients with constipation. Despite the lack of clear-cut effects on colonic transit and defecation, this treatment seems to be associated with a relief of symptoms. However, due to a very limited number of patients, this study was underpowered to show a clear-cut effect of dexloxiglumide on symptoms¹². Moreover the authors suspect that CCK-1 intron polymorphism may also influence the response to CCK-1 antagonist therapy.

Nevertheless, a 12-wk, phase-II trial of dexloxiglumide in IBS has shown that in female constipated IBS patients, dexloxiglumide 200 mg/day was associated with higher proportion of improvement in abdominal pain and discomfort from baseline compared to placebo¹³.

All these data support an important role of CCK₈ or an alteration of the CCK receptor distribution in Functional Bowel Disorders suggesting that CCK antagonists may be promising agents in the treatment of these functional diseases and particularly IBS.

REFERENCES

1. Bueno L, et al. *Science* 1982;216:1427-9.
2. Coffin B, Fossati S, Flourie B, et al. Regional effects of cholecystokinin octapeptide on colonic phasic and tonic motility in healthy humans. *Am J Physiol* 1999;276:G767-72.
3. O'Brien MD, Camilleri M, Thomforde GM, Wiste JA, Hanson RB, Zinsmeister AR. Effect of cholecystokinin octapeptide and atropine on human colonic motility, tone, and transit. *Dig Dis Sci* 1997; 42:26-33.
4. Boulant J, Mathieu S, D'Amato M, Abergel A, Dapoigny M, Bommelaer G. Cholecystokinin in transient lower oesophageal sphincter relaxation due to gastric distension in humans. *Gut* 1997;40:575-81.
5. Lopez Y, Fioramonti J, Bueno L. Central and peripheral control of postprandial pyloric motility by endogenous opiates and cholecystokinin in dogs. *Gastroenterology* 1991;101:1249-55.
6. Rastegar H, Homayoun H, Afifi M, Rezayat M, Dehpour AR. Modulation of cholestasis-induced antinociception by CCK receptor agonists and antagonists. *Eur Neuropsychopharmacol* 2002;12:111-8.

Lectures

7. Hawranko AA, Smith DJ. Stress reduces morphine's antinociceptive potency: dependence upon spinal cholecystokinin processes. *Brain Res* 1999; 824:251-7.
8. Magnuson DS, Sullivan AF, Simonnet G, Roques BP, Dickenson AH. Differential interactions of cholecystokinin and FLFQPQRF-NH₂ with mu and delta opioid antinociception in the rat spinal cord. *Neuropeptides* 1990;16:213-8.
9. Roberts-Thompson 1992.
10. Sabate JM, Gorbachev C, Flourie B, Jian R, Coffin B. Cholecystokinin octapeptide increases rectal sensitivity to pain in healthy subjects. *Neurogastroenterol Motil* 2002;14:689-95.
11. Cann PA, et al. *Gastroenterology* 1993 ; 104 : A486.
12. Cremonini F, Camilleri M, McKinzie S, et al. Effect of CCK-1 antagonist, dexloxiglumide, in female patients with irritable bowel syndrome: a pharmacodynamic and pharmacogenomic study. *Am J Gastroenterol* 2005;100:652-63.
13. D'Amato M, et al. *Gut* 1999;45(Suppl V):A258.

OPIOID SYSTEM AND GASTROINTESTINAL FUNCTION: NEW PERSPECTIVES FOR DRUG DEVELOPMENT

C SCARPIGNATO

Laboratory of Clinical Pharmacology,
School of Medicine & Dentistry University of Parma,
Parma, Italy

Endogenous opioids (enkephalins, beta-endorphins, endomorphins and dynorphins) play a major role in the control of gastrointestinal (GI) function and dysfunction, including gut motility, epithelial transport and visceral sensitivity¹. These peptides are located in specific sites of the brain, spinal cord, autonomic ganglia and, within the GI tract, at the level of the enteric nervous system (ENS)². Three distinct opioid receptors [MOP (μ), DOP (δ), KOP (κ)] are expressed throughout the Central Nervous System (CNS) and in peripheral regions, including the digestive system. They all belong to the large superfamily of seven transmembrane-spanning (7TM) G protein-coupled receptors and their stimulation is followed by inhibition of adenylate cyclase with reduction of intracellular c-AMP³. These three receptors correspond to the classical opioid receptors that mediate analgesia induced by exogenous opioid drugs. Recently, a 17-amino acid neuropeptide, nociceptin/orphanin FQ (N/OFQ) has been identified as the endogenous ligand for the opioid receptor-like 1 (ORL-1) receptor (also referred as NOP receptor). Although ORL-1 belongs to the opioid receptor family, it does not bind classical opioids, displays a hyperalgesic effect and the ORL-1-N/OFQ system has pharmacological actions distinct from those of the opioid receptor system^{3,4}. While recent evidence suggests that central ORL-1 receptors are involved in a variety of functions within the GI tract (like nociception, food intake and GI motility), the role of peripheral ones is largely unknown. Another putative receptor, the existence of which has long been controversial, is the ϵ -opioid receptor selectively stimulated supraspinally by the beta-endorphin to produce antinociception^{3,5}. However, this receptor is poorly characterized, and proof for its existence through identification of the respective gene is still lacking³.

The constipating effect of morphine and the opiates represent a major drawback in the long-term use of these compounds for the control of chronic pain⁶. Generally, these drugs interfere with normal GI motility by delaying transit, by stimulating non-propulsive motility, segmentation and tone and by contracting alimentary sphincters such as the pylorus^{6,7}. All these effects are mainly mediated by κ - and μ -receptors. Opioids also inhibit secretion probably via serotonin release from tryptaminergic neurons and stimulate absorption of fluids, mainly as a result of a delayed transit, although a stimulation of water and electrolyte absorption independent from the motor effects and mediated via activation of epithelial δ -receptors has been demonstrated. The net result of these multiple effects on absorption and secretion are reduced stool water content and harder stools, leading to the well-known opioid-induced constipation⁷. However, constipation is just one symptom of an often under-recognized condition known as opioid-induced bowel dysfunction (OBD), whose manifestations also include incomplete evacuation, abdominal distension,

bloating, abdominal discomfort and increased gastro-oesophageal reflux and which may lead to secondary complications such as pseudo-obstruction of the bowel, nausea, vomiting as well as interference with oral drug administration and absorption⁸.

The precise knowledge of opioid mechanisms of action on gut functions has allowed the development of selective agonists and antagonists either to manage clinical conditions such as diarrhoea, constipation and irritable bowel syndrome (IBS) or to counterbalance OBD without interfering with the central analgesic activity of these drugs. Loperamide and diphenoxylate, two synthetic μ -opioid agonists, are widely used as antidiarrhoeal drugs^{7,9}. Unlike diphenoxylate or codeine, **loperamide** does not cross blood-brain barrier or exert any opiate activity in man at normal therapeutic doses. The mechanism of action of loperamide is primarily the retardation of small-intestinal transit *via* stimulation of μ -receptors in the myenteric plexus, and the stimulation of anal sphincter pressure and of faecal continence¹⁰. This mechanism increases mucosal contact time, allowing more complete absorption of electrolytes and water. Besides its opiate-receptor binding and stimulating activity, loperamide also behaves as a calcium-calmodulin antagonist and as a calcium channel blocker¹⁰. These two other mechanisms might contribute to loperamide's antidiarrhoeal activity. Stimulation of δ -receptors by selective antagonists, like **BW 942C** (a synthetic met-enkephalin derivative) appears to be an effective approach to the treatment of diarrhoea as it is the combined μ and δ -receptor stimulation with **nufenoxole** (SC-27166)¹¹. An indirect approach to the modulation of opioid pathways to treat diarrhoea is to potentiate the effect of the endogenous enkephalins, which activate δ -receptors at the basolateral membrane of the enterocyte, resulting in an inhibition of adenylate cyclase^{11,12}. Under physiological conditions, endogenous opioids are rapidly degraded by the cell membrane peptidase enzyme enkephalinase. Enkephalinase inhibition by **raccadotril** (previously known as acetorphan) results in a prolonged antisecretory effect comparable to that of loperamide but less often followed by rebound constipation¹².

Drugs with selectivity for one of the opioid receptors have not, as yet, yielded the ideal analgesic, as many of the GI adverse effects of opioid drugs are mediated by the same receptor that produces analgesia (the MOP or μ -receptor). Selective agonists at non- μ sub-types of opioid receptors do not exert useful global analgesic properties. Although with newer derivatives, like **dihydroetorphine**¹³, the incidence of constipation is significantly reduced, OBD remains a major clinical challenge. Selective blockade of peripheral μ -receptors should be able to prevent or reverse the adverse effects of opioid drugs on the GI tract. However, currently marketed opioid receptor antagonists also cross the blood-brain barrier and enter the brain where they can block the primary pain relieving effects of opioid analgesics such as morphine. These findings have created the opportunity to develop a new class of opioid antagonists which, when taken with opioid analgesics, are designed to block their side effects on the GI tract but not the desired analgesic activity. While **methylnaltrexone**¹⁴ is a quaternary ammonium derivative of naltrexone, an opioid antagonist similar to naloxone but less lipid soluble and thus less likely to cross the blood-brain barrier, **alvimopan**¹⁵ is a selective peripherally acting μ -receptor antagonist. Both compounds reduce opioid-induced

bowel symptoms without antagonizing centrally mediated analgesic effects⁸. Since endogenous opioids are elevated following surgery, selective peripheral blockade of μ -receptors was also tested in post-operative bowel dysfunction. Alvimopan proved to be capable of relieving symptoms of postoperative ileus, shorten hospitalization and speeding recovery of bowel function⁸. This drug also increases transit in the ascending colon of healthy individuals¹⁵. Likewise, preliminary data suggests that alvimopan may reduce whole bowel transit time in patients with chronic constipation¹⁶ or IBS and constipation (C-IBS)¹⁷. In line with these results, an enteric-coated formulation of **naloxone** proved to be beneficial in constipated IBS patients¹⁸. Taken together, these data suggest that peripheral opioid antagonists may be effective prokinetics¹⁹.

Trimebutine, a weak non selective opioid agonist unable to cross blood-brain barrier, has long been used in the treatment of functional bowel disease²⁰ and found to be an effective antispasmodic in IBS²¹. Recently, some peripherally acting κ -agonists have been developed to avoid their CNS effects, mainly dysphoria and hallucinations²². Peripheral κ opioid agonists are not associated with GI dysmotility but they do have anti-nociceptive effects in the GI tract. For example, preclinical studies suggest that peritoneal irritation induced pain is reversed with a κ agonist. Likewise, κ opioid agonists inhibit the response of peripheral primary afferents to colorectal distention^{9,23}. A non-opioid mechanism via sodium channel blocking properties has been proposed for κ opioid agonists suggesting that these agents may also act as a local anesthetic^{22,23}. **Fedotozine** was the first κ agonist studied in humans. In clinical trials it proved to be better than placebo in relieving bloating, abdominal pain, postprandial fullness and nausea in patients with functional dyspepsia (FD) while it was slightly superior to placebo in getting symptom relief in patients with IBS^{9,24}. **Asimadoline** (EMD 61,753) is another peripheral κ agonist, which – after single dose administration – was able to reduce perception of gas in response to colonic distension²⁵ and decrease satiety and postprandial symptoms after a liquid meal²⁶. This drug therefore deserves to be studied in both IBS and FD. Finally, preliminary results of a study with a new peripheral κ opioid agonist, **ADL 10-0101**, showed it to be effective in reducing pain in patients suffering from chronic pancreatitis²⁷.

In conclusion, a new generation of peripheral opioid receptor ligands devoid of central CNS side effects is being developed for the treatment of GI disorders and appears promising for the management of both opioid-induced dysfunction and idiopathic functional GI disease.

REFERENCES

1. Greenwood-Van Meerveld B, Gardner CJ, Little PJ, Hicks GA, Dehaven-Hudkins DL. Preclinical studies of opioids and opioid antagonists on gastrointestinal function. *Neurogastroenterol Motil* 2004; 16 (Suppl 2):46-53.
2. Sternini C, Patierno S, Selmer IS, Kirchgessner A. The opioid system in the gastrointestinal tract. *Neurogastroenterol Motil* 2004;16(Suppl 2):3-16.
3. Waldhoer M, Bartlett SE, Whistler JL. Opioid receptors. *Annu Rev*

Lectures

- Biochem 2004;73:953-990.
4. New DC, Wong YH. The ORL1 receptor: molecular pharmacology and signalling mechanisms. *Neurosignals* 2002;11:197-212.
 5. Tseng LF. Evidence for epsilon-opioid receptor-mediated beta-endorphin-induced analgesia. *Trends Pharmacol Sci* 2001;22:623-630.
 6. De Luca A, Coupar IM. Insights into opioid action in the intestinal tract. *Pharmacol Ther* 1996;69:103-115.
 7. De Schepper HU, Cremonini F, Park MI, Camilleri M. Opioids and the gut: pharmacology and current clinical experience. *Neurogastroenterol Motil* 2004;16:383-394.
 8. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs* 2003;63:649-671.
 9. Corazziari E. Role of opioid ligands in the irritable bowel syndrome. *Can J Gastroenterol* 1999;13(Suppl A):71A-75A.
 10. Huijghebaert S, Awouters F, Tytgat GN. Racecadotril versus loperamide: antidiarrheal research revisited. *Dig Dis Sci* 2003;48:239-250.
 11. Scarpignato C, Rampal P. Prevention and treatment of traveler's diarrhea: a clinical pharmacological approach. *Chemotherapy* 1995;41(Suppl 1):48-81.
 12. Matheson AJ, Noble S. Racecadotril. *Drugs* 2000;59:829-835.
 13. Ohmori S, Morimoto Y. Dihydroetorphine: a potent analgesic: pharmacology, toxicology, pharmacokinetics, and clinical effects. *CNS Drug Rev* 2002;8:391-404.
 14. De Ponti F. Methylalntrexone Progenics. *Curr Opin Investig Drugs* 2002;3:614-620.
 15. Camilleri M. Alvimopan, a selective peripherally acting mu-opioid antagonist. *Neurogastroenterol Motil* 2005;17:157-165.
 16. Garnett W, Kelleher D, Hickmott F, et al. Alvimpan (ALV) shortens whole bowel transit time in adults with chronic constipation (CC). *Gastroenterology* 2004;126(Suppl 2):A643.
 17. Gonenne J, Ferber I, Burton D, et al. Effect of the peripheral mu-opioid antagonist, alvimopan, on gastrointestinal transit in health: reversal of codeine effects and stimulation of colonic transit. *Gastroenterology* 2005;128(Suppl 2):A106.
 18. Hawkes ND, Rhodes J, Evans BK, Rhodes P, Hawthorne AB, Thomas GA. Naloxone treatment for irritable bowel syndrome - a randomized controlled trial with an oral formulation. *Aliment Pharmacol Ther* 2002;16:1649-1654.
 19. Holzer P. Opioids and opioid receptors in the enteric nervous system: from a problem in opioid analgesia to a possible new prokinetic therapy in humans. *Neurosci Lett* 2004;361:192-195.
 20. Delvaux M, Wingate D. Trimebutine: mechanism of action, effects on gastrointestinal function and clinical results. *J Int Med Res* 1997;25:225-246.
 21. Poynard T, Regimbeau C, Benhamou Y. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2001;15:355-361.
 22. Barber A, Gottschlich R. Novel developments with selective, non-peptidic kappa-opioid receptor agonists. *Expert Opin Investig Drugs* 1997;6:1351-1368.
 23. Junien JL, Riviere P. Review article: the hypersensitive gut - peripheral kappa agonists as a new pharmacological approach. *Aliment Pharmacol Ther* 1995;9:117-126.
 24. Delvaux M. Pharmacology and clinical experience with fedotozine. *Expert Opin Investig Drugs* 2001;10:97-110.
 25. Delvaux M, Beck A, Jacob J, Bouzamondo H, Weber FT, Frexinos J. Effect of asimadoline, a kappa opioid agonist, on pain induced by colonic distension in patients with irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;20:237-246.
 26. Delgado-Aros S, Chial HJ, Cremonini F, et al. Effects of asimadoline, a kappa-opioid agonist, on satiation and postprandial symptoms in health. *Aliment Pharmacol Ther* 2003;18:507-514.
 27. Eisenach JC, Carpenter R, Curry R. Analgesia from a peripherally active kappa-opioid receptor agonist in patients with chronic pancreatitis. *Pain* 2003;101:89-95.

Abstracts

- *Index*
- *Summaries*

	<i>Page</i>
1 • HOSPITAL ADMISSIONS FOR FUNCTIONAL DIGESTIVE DISORDERS IN ITALY DURING YEARS 1999-2003 D FRANCIOTTI <i>First Aid and Admission Service of the ASL of Teramo, Teramo, Italy</i>	68
2 • GASTROINTESTINAL DYSMOTILITY AND MULTIPLE SCLEROSIS HV VATEV <i>I.R.M., Rome, Italy</i>	68
3 • ALEXITHYMIA AND PSYCHOPATHOLOGY IN PATIENTS WITH PSYCHIATRIC AND FUNCTIONAL GASTROINTESTINAL DISORDERS M DE CARNE ¹ AND P PORCELLI ² <i>Department of¹Gastroenterology and²Psychosomatic Unit, IRCCS “de Bellis” Hospital, Castellana Grotte (BA), Italy</i>	69
4 • FUNCTIONAL HEARTBURN IS COMMON IN ASIAN PATIENTS WITH NON-EROSIVE REFLUX DISEASE N-M LAW <i>Motility & Endoscopy Research Centre, Singapore General Hospital, Singapore</i>	69
5 • SYMPTOM INDEX IDENTIFIED MORE PATIENTS WITH NON-EROSIVE REFLUX DISEASE WITH ATYPICAL SYMPTOMS N-M LAW ¹ , A HSU ² , C-M LOO ² , C LO ² , Y-M CHAN ³ , N-G TAN ³ <i>¹Motility & Endoscopy Research Centre, ²Department of Respiratory Medicine, ³Department of ENT Singapore General Hospital, Singapore</i>	70
6 • WATER LOAD TEST BEFORE AND AFTER PPI-THERAPY IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE E BATTAGLIA ¹ , M GRASSINI ¹ , P NIOLA ¹ , C VERNA ¹ , M NAVINO ² , L DUGHERA ² , G EMANUELLI ² , G BASSOTTI ³ <i>¹Gastroenterology and Endoscopy Unit, Cardinal Massaia Hospital, Asti, Italy; ²Department of Gastroenterology, San Giovanni Battista Hospital, Turin, Italy; ³Department of Clinical and Experimental Medicine, University of Perugia, Italy</i>	70
7 • SCINTIGRAPHIC STUDY IN CHILDREN WITH GASTRO-OESOPHAGEAL REFLUX DISEASE AND DELAYED GASTRIC EMPTYING: EVALUATION OF A HIGH-EFFECTIVE SURGICAL TREATMENT T CALDARO ¹ , L DALL’OGLIO ¹ , P DE ANGELIS ¹ , MC GARGANESE ² , F TORRONI ¹ , A PANE ¹ , G FEDERICI DI ABRIOIA ¹ , G CIOFETTA ² <i>¹Digestive Surgical and Endoscopic Unit, ²Nuclear Medicine Unit, “Bambino Gesù” Children’s Hospital-IRCCS, Rome, Italy</i>	71
8 • MECHANISMS OF POSTOPERATIVE DYSMOTILITY IN THE SMALL INTESTINE ASSOCIATED WITH INTERSTITIAL CELLS OF CAJAL AND PROTECTIVE EFFECTS OF INDUCIBLE NITRIC OXIDE INHIBITION H YANAGIDA ¹ , KM SANDERS ² AND SM WARD ² <i>¹Division of Neuroscience, JCSMR, The Australian National University, Canberra, Australia, ²Department of Physiology and Cell Biology, University of Nevada, Reno, NV, USA</i>	71

Index

	<i>Page</i>
9 • CAPSULE ENDOSCOPY AND NON-HAEMORRAGIC SMALL BOWEL DISEASES; PRELIMINARY RESULTS F BONFANTE, M TEBALDI, S PISTOSO AND W PIUBELLO <i>Department of Internal Medicine and Endoscopic Unit, Hospital of Desenzano del Garda (BS), Italy</i>	72
10 • EFFICIENCY OF ADDING 6 MERCAPTOPURINE (6 MP) IN CORTICODEPENDENT ULCERATIVE COLITIS AND EFFICIENCY OF INFLIXIMAB (INFL) IN REFRACTORY ULCERATIVE COLITIS (UC) D OLTEANU, D LUPU, M ABBAS <i>Internal Medicine I, University Hospital, Bucharest, Romania</i>	72
11 • SMAD3-KNOCKOUT MICE LACK INTERSTITIAL CELLS OF CAJAL IN THE COLONIC WALL G LATELLA ¹ , A VETUSCHI ² , R SFERRA ² , A D'ANGELO ¹ , V CATITTI ¹ , G ZANNINELLI ¹ , M CHIARAMONTE ¹ , R CAPRILLI ³ , E GAUDIO ⁴ ¹ <i>Cattedra di Gastroenterologia, Università degli Studi di L'Aquila, Italy</i> ² <i>Cattedra di Anatomia Umana, Università degli Studi di L'Aquila, Italy</i> ³ <i>Cattedra di Gastroenterologia I, Università degli Studi di Roma "La Sapienza", Italy</i> ⁴ <i>Cattedra di Anatomia Umana, Università degli Studi di Roma "La Sapienza", Italy</i>	73
12 • COLONIC MUSCLE CELL DAMAGE INDUCED BY EXPOSURE OF HUMAN MUCOSA TO A PATHOGENIC LIPOPOLYSACCHARIDE IS MEDIATED BY OXIDATIVE STRESS AND BY PROSTAGLANDINS M GUARINO ¹ , S CAROTTI ¹ , C SEVERI ² , G DI CUONZO ³ , I TATTOLI ² , R ALLONI ¹ , AM ALTOMARE ¹ , M CICALA ¹ ¹ <i>Dpt of Digestive Diseases of Campus Biomedico University</i> ² <i>Dpt of Clinical Sciences, University La Sapienza</i> ³ <i>Dpt of Laboratory Medicine, Campus Biomedico University, Rome, Italy</i>	73
13 • PATIENTS WITH CLINICALLY DIFFERENT SYMPTOM-BASED DIAGNOSIS OF FUNCTIONAL BOWEL DISORDERS MAY HAVE IDENTICAL SPECIFIC AND NON SPECIFIC ILEO-COLO-RECTAL MICROSCOPIC ABNORMALITIES A MARCHEGGIANO ¹ , A COVOTTA ² , C IANNONI ¹ , D BADIALI ¹ , R CANTARINI ¹ , M PAOLETTI ² , N PALLOTTA ¹ , E CORAZZIARI ¹ ¹ <i>Dept Scienze Cliniche, University "La Sapienza", Rome, Italy</i> ² <i>Department of Surgical Sciences, University "La Sapienza", Rome, Italy</i>	74
14 • RISK FACTORS OF IRRITABLE BOWEL SYNDROME (IBS) - LIKE SYMPTOMS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD) C FIERBINTEANU-BRATICEVICI ¹ , L TRIBUS ¹ , P DRAGOMIR ¹ , T BADESCU ² , D ANDRONESCU ¹ . ¹ <i>Medical Clinic II, Department of Gastroenterology, University Hospital, Bucharest</i> ² <i>Medical Clinic, Department of Gastroenterology Bucharest, Romania</i>	74
15 • ULTRASOUND EVALUATION IN DIAGNOSIS AND FOLLOW-UP OF ACUTE COLONIC DIVERTICULITIS C FIERBINTEANU-BRATICEVICI, L NEGREANU, A BENGUS, R USVAT, D ANDRONESCU <i>Medical ClinicII, Department of Gastroenterology, University Hospital, Bucharest, Romania</i>	75

	<i>Page</i>
16 • SYMPTOMATIC CHARACTERIZATION OF UNCOMPLICATED COLON DIVERTICULAR DISEASE F DE GIORGI ¹ , F BACCINI ² , G MACONI ³ , A RISPO ⁴ , L PASQUALE ⁴ , G SARNELLI ¹ , B ANNIBALE ² , R CUOMO ¹ . ¹ <i>Gastroenterologia, Dipartimento Medicina Clinica e Sperimentale, AOU Federico II Napoli, Italy</i> ² <i>Dipartimento di Malattie Digestive, Ospedale S.Andrea, Università La Sapienza, Roma, Italy</i> ³ <i>Dipartimento di Gastroenterologia, Ospedale Universitario L.Sacco, Milano, Italy;</i> ⁴ <i>U.O. di Gastroenterologia, ASL AV1, P.O. Ariano Irpino (AV), Italy</i>	75
17 • RECTOCELE AND INTRARECTAL/ANAL INTUSSUSCEPTION ARE NOT RELATED WITH IMPAIRED RECTAL TRANSIT AND EMPTYING, IN FUNCTIONAL CONSTIPATION F ALGHISI, D BADIALI, R CAPPUCCIO, F ANZINI, E CORAZZIARI, FI HABIB <i>Department Clinica Sciences, University "La Sapienza", Rome, Italy</i>	76
18 • HISTOCHEMISTRY IN HIRSCHSPRUNG'S DISEASE: THE NEW ERA OF DIAGNOSTIC KITS G MARTUCCIELLO ¹ , F VENERUCCI ² , C SBONA ² ¹ <i>IRCCS Policlinico S.Matteo, Pavia, Italy;</i> ² <i>Bio-Optica, Milan, Italy</i>	76
19 • A NEW MINI-INVASIVE TECHNIQUE TO OBTAIN FULL-THICKNESS COLON BIOPSIES VIA ONE-TROCAR TRANSUMBILICAL LAPAROSCOPY FOR DIAGNOSIS OF COMPLEX ENTERIC NERVOUS SYSTEM ABNORMALITIES G MARTUCCIELLO, P ROMANO <i>Dept Paediatric Surgery "IRCCS Policlinico San Matteo" Pavia, Italy</i>	77
20 • DO RADIO OPAQUE TRANSIT STUDIES PREDICT QUALITY OF LIFE IN PATIENTS WITH CHRONIC CONSTIPATION? S COWLAM ¹ , D WOOFF ² , I MINTY ¹ , S GREEN ¹ , J VARMA ¹ , Y YIANNAKOU ¹ ¹ <i>University Hospital of North Durham,</i> ² <i>Statistics & Mathematics Unit University of North Durham, Durham, UK</i>	77
21 • PHENOTYPIC VARIATION IN DISORDERS OF DEFECATION IN SPINAL CORD INJURED PATIENTS G BAZZOCCHI, PF ALMERIGI, E POLETTI, P PILLASTRINI, M MENARINI <i>Montecatone Rehabilitation Institute S.p.A. - University of Bologna, Italy</i>	78
22 • EFFECT OF A NEW TRANS ANAL IRRIGATION METHOD ON COLONIC CLEARING OF RADIOOPAQUE MARKERS IN PATIENTS WITH SEVERE CONSTIPATION G BAZZOCCHI, PF ALMERIGI, E POLETTI, P PILLASTRINI, M MENARINI <i>Montecatone Rehabilitation Institute S.p.A. - University of Bologna, Italy</i>	78
23 • MEDICAL TREATMENT OF ENCOPRESIS IN CONSTIPATED CHILDREN F BRACCI, D BADIALI, F ANZINI, E CORAZZIARI <i>Department of Clinical Sciences, University "La Sapienza" Rome, Italy</i>	79
24 • CHRONIC CONSTIPATION: RESULTS OF A CLINICAL OBSERVATION IN THE USE OF FR.E.M.S. (FREQUENCY MODULATED ELECTROMAGNETIC NEURAL STIMULATION) THERAPY. PILOT STUDY M MASSARI ^{1,3} , A ZANELLA ² , P DESIDERI ³ , G RANDO ¹ , A WIEL MARIN ¹ ¹ <i>Department of Surgical Sciences, U.O.C. General Surgery 1, Catholic University S. Heart-Columbus Hospital Rome;</i> ² <i>Lorenz Biotech, Medolla, Modena</i> ³ <i>Ce.Te.Ri. Rehabilitation Therapy Centres, Onlus, Rome, Italy</i>	79

HOSPITAL ADMISSIONS FOR FUNCTIONAL DIGESTIVE DISORDERS IN ITALY DURING YEARS 1999-2003

D Franciotti

First Aid and Admission Service of the ASL of Teramo, Teramo, Italy

In Italy (Italian Ministry of Health data bank) during years 1999-2003 owing to the studied pathologies a total amount of 132,955 patients has been admitted: 55,439 males and 77,516 females. Total amount of yearly admissions owing to the same pathologies has decreased from 1999 to 2003: 32,176 in 1999 versus 22,464 in 2003. The calculated mean national rate of hospital admission because of the studied pathologies amounts to 46.5/100,000 (highest rate of 56.45/100,000 recorded in 1999 and lowest rate of 36.45/100,000 recorded in 2003). The mean national rate of admission has amounted to 40.18/100,000 as to the males and to 52.71/100,000 as to the females (highest rates of 48.62/100,000 as to the males and of 63.79/100,000 as to the females recorded in 1999, lowest rates of 33.65/100,000 as to the males and of 44.81/100,000 as to the females recorded in 2003). The two age ranges < 1 year to 15 years and that > 65 years to > 75 years have been those with the highest rates of admission. The age range with the lowest rate of admission has been that between 25 and 44 years. The regions located at the South of Italy are those where the greatest rates of admission have been recorded, with a maximum rate of 129.40/100,000 in 1999 and of 94.95/100,000 in 2003 recorded in the region Calabria. The research shows that the hospital admissions owing to the studied pathologies in Italy have decreased in the last years and that they mainly affect female, young and old subjects resident in southern regions of Italy. The study may indirectly suggest that the so far classified functional disorders of gastrointestinal system could be related to sex, age and geographic factors.

P1

GASTROINTESTINAL DYSMOTILITY AND MULTIPLE SCLEROSIS

HV Vatev

C.I.R.M., Rome, Italy

This study investigated the physiology of patients affected from Multiple Sclerosis (age between 25 and 57 years) and has supplied data that demonstrate:

- The severity of the neurological symptoms does not keep up a correspondence to the dimension of the lesion evidenced by the Nuclear Magnetic Resonance;

● All of the patients presented gastro-intestinal dysmotility. The study lead by us, has evidenced that the combination between the reduced conduction velocity of the impulse along the nervous fiber (caused by loss of myelin) together with other deficit caused by the MS (progressive weakness, ataxia etc.) gives place to Gastrointestinal Dysmotility.

This syndrome, that we would want to propose with the name of Neurogenic Gastrointestinal Tract in MS, manifests with:

- Dysphagia
- Delayed gastroesophageal transit time
- Decreased function of the gastric pacemaker
- Diminished amplitude of peristaltic contractions
- Delayed gastric emptying
- Reduced peristaltic activity
- Incomplete sphincter relaxations
- Delayed emptying of the cecum and the ascending colon
- Dysbiosis
- Dyssynergia of the pelvic floor
- Dysfunction of the internal anal sphincter

These phenomena can be recorded and identified with the existing techniques.

An integrative approach is indispensable towards the patients affected from MS and not only for the reason that we have the responsibility to study the complete clinical picture, but also because the Gastrointestinal Dysmotility has an important impact on the quality of life, and maybe also on the course of the chronic disease.

P2

ALEXITHYMIA AND PSYCHOPATHOLOGY IN PATIENTS WITH PSYCHIATRIC AND FUNCTIONAL GASTROINTESTINAL DISORDERS

M. De Carne¹ and P. Porcellì²

Department of ¹Gastroenterology and ²Psychosomatic Unit, IRCCS “de Bellis” Hospital, Castellana Grotte, Bari, Italy.

Background. Alexithymia and psychopathology may influence the way individuals experience psychological distress and somatic symptoms. This study evaluated patients referred to psychiatric and gastroenterologic outpatient settings in order to investigate the levels of alexithymia and psychopathology, and the possible role of alexithymia in symptom perception and health care utilization. The association between psychiatric disorders and functional gastrointestinal disorders (FGIDs) was also assessed.

Methods. Psychopathology, alexithymia and gastrointestinal symptoms were evaluated in 52 psychiatric outpatients and 58 medical outpatients with FGIDs. Two comorbid subgroups of 25 psychiatric patients with FGIDs and 38 FGID patients were formed and compared.

Results. Forty-eight percent of the psychiatric patients had associated FGIDs and 65.5% of the FGID patients had associated psychiatric disorders. The FGID patients had significantly less psychopathology, but significantly higher alexithymia and more severe gastrointestinal symptoms, than the psychiatric patients. In the comparison of the two subgroups with comorbidity, FGID patients with psychiatric disorders were still more alexithymic and had less psychopathology than psychiatric patients with FGIDs, but gastrointestinal symptoms were not significantly different.

Conclusion. Patients with functional gastrointestinal symptoms attending a medical care service are likely to be highly alexithymic, whereas those attending a psychiatric care service are likely to show severe psychopathology. Alexithymia seems to influence the presentation of functional somatic symptoms and the type of health care utilization.



FUNCTIONAL HEARTBURN IS COMMON IN ASIAN PATIENTS WITH NON-EROSIVE REFLUX DISEASE

N-M Law

Motility & Endoscopy Research Centre, Singapore General Hospital, Singapore

Background. The diagnosis of Non-Erosive Reflux Disease (NERD) is a clinical challenge. We have recently reported that the wireless Bravo™ pH system increased the diagnostic yield for these patients. Functional Heartburn is a subgroup of NERD and is defined as an episodic retrosternal burning in the absence of pathological gastro-oesophageal reflux, pathology based motility disorders or structural explanations. We hypothesized that by conducting prolonged oesophageal pH studies, we would be able to differentiate patients with Functional Heartburn as defined by normal acid exposure during pH studies. **Method.** We reported our findings on prolonged esophageal pH studies using the wireless Bravo™ pH system on 18 patients with NERD. All these patients had significant reflux symptoms and negative endoscopy. All patients were initially studied for 2 days with the wireless Bravo™ pH system following a standard protocol. The pH data were uploaded and the receiver batteries were changed on the third days. Once we have confirmed that the pH capsules remained attached, a further period of 2 days of pH studies was performed. We were able to complete a total of 3 and 4 days of pH recording for 5 and 13 patients respectively. An abnormal oesophageal acid exposure was defined by a total fraction time of more than 4 % with pH < 4 in a 24-hour period. Symptom Association Probability (SAP) of > 95% was considered positive for acid related reflux symptoms.

Results. Three groups of patients with NERD were identified. Only 8 patients (44%) had abnormal acid exposure. The remaining 10 patients (56%) were diagnosed to have Functional Heartburn. Seven out of these 10 patients showed positive SAP indicating that they have acid related Functional Heartburn. In contrast, 3 patients with normal pH and negative SAP might have non-acid related Functional Heartburn. In addition, abnormal acid exposure and SAP were detected in 4 and 3 patients respectively only when the studies were continued beyond the third day. In summary, the first 48 hours of pH recording only diagnosed 61% of patients with NERD.

Conclusion. Our study showed that Functional Heartburn is common in our Asian patients with NERD. Prolonged oesophageal pH studies up to 4 days have enabled us to differentiate patients into subgroups of NERD. This may have significant therapeutic impact as some patients with Functional Heartburn do not response to high dose PPI alone.

SYMPTOM INDEX IDENTIFIED MORE PATIENTS WITH NON-EROSIVE REFLUX DISEASE WITH ATYPICAL SYMPTOMS

N-M Law¹, A Hsu², C-M Loo², C Lo², Y-M Chan³, N-G Tan³

¹Motility & Endoscopy Research Centre, ²Department of Respiratory Medicine, ³Department of ENT, Singapore General Hospital, Singapore

Background. The diagnosis of GERD with atypical symptoms and negative endoscopy is a clinical challenge. Twenty-four hour oesophageal pH study has been widely used to diagnose acid reflux in these patients. We hypothesised that measuring acid exposure alone may be inadequate and Symptom Index may be needed in order to increase the diagnostic yield of GERD.

Methods. We conducted a prospective study on 30 patients with atypical reflux symptoms presenting as chest and ENT symptoms with negative evaluation for lung and ENT diseases. All patients had no typical reflux symptoms with negative endoscopy. Twenty-four hour oesophageal pH study was performed with solid-state catheter with the pH sensor located 5 cm above the LES predetermined by oesophageal manometry. The diagnosis of significant GERD was based on a DeMeester score of > 14.72. Symptom Index (SI) was calculated as: $SI = (\text{Number of reflux-related symptom episodes} / \text{Total number of symptom episodes}) \times 100\%$. Significant acid reflux is defined as SI of > 50% based on our previous observations.

Results. Using DeMeester score alone, only 30% of patients were positive for GERD with a mean DeMeester score of 34.7 (range: 15.1-73.2). In contrast, 65% of patients was found to have a positive SI with a mean score of 73% (range: 55- 100%). All patients tested positive for either score were put on intensive PPI therapy for at least 3 months. At the end of the 6 months study period, 95% of the patients with positive pH study and 90% of patients with positive SI had resolution of their symptoms. The response to treatment was not statistically different between the two groups.

Conclusions. Twenty-four hour esophageal pH study should routinely be done in patients with atypical reflux symptoms and negative endoscopy. Besides using conventional acid exposure indices, determination of Symptom Index enabled the identification of additional patients who will benefit from aggressive acid suppression therapy.

P4

WATER LOAD TEST BEFORE AND AFTER PPI-THERAPY IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE

E. Battaglia¹, M. Grassini¹, P. Niola¹, C. Verna¹, M. Navino², L. Dughera², G. Emanuelli², G. Bassotti³

¹Gastroenterology and Endoscopy Unit, Cardinal Massaia Hospital, Asti, Italy

²Department of Gastroenterology, San Giovanni Battista Hospital, Turin, Italy

³Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy

Background. Visceral hypersensitivity has been identified as an important pathophysiologic mechanism in patients with gastroesophageal reflux (GERD), not well controlled by usual therapy. To assess the visceral perception and its relationship to therapy, we used the water load test (WLT) in patients with GERD.

Methods. A symptom visual analogue scale (VAS, 0-10 cm) and 5 min-WLT was used to evaluate symptom sensitivity (heartburn, postprandial fullness, vomiting, early satiety, nausea, bloating, epigastric pain, belching, epigastric burning) in 10 healthy controls (HC, 5F/5M, mean age 42+6 yrs) and 12 patients with GERD (8F/4M, mean age 40+5 yrs), before and after therapy (esomeprazole, 40 mg/day for four weeks).

Results. Before therapy, HC drank more water than GERD patients (588+42 ml vs 497+38 ml), without significant differences between men and women. GERD patients showed basally a significant correlation between WLT and symptoms VAS with respect to heartburn ($p < 0.05$), nausea ($p < 0.02$) and belching ($p < 0.05$). After 4-weeks PPI-therapy 7 GERD patients had significant improvement of the symptom VAS ($p < 0.001$) and only a little increment of the volume of water ingested (501+11). 5 GERD patients did not refer significant amelioration of the symptom VAS, and in 4 of them a significant correlation ($p < 0.05$) with WLT and symptoms VAS for post-prandial fullness and nausea was shown.

Conclusions. GERD patients display gastric hypersensitivity compared to healthy controls concerning the water load test. This test can be useful to discriminate the GERD-subgroups that potentially not improve symptoms after the first step therapy, possibly due to an overlap with functional dyspepsia.

P5

SCINTIGRAPHIC STUDY IN CHILDREN WITH GASTRO-OESOPHAGEAL REFLUX DISEASE AND DELAYED GASTRIC EMPTYING: EVALUATION OF A HIGH-EFFECTIVE SURGICAL TREATMENT

T Caldaro, L Dall'Oglio, P De Angelis, MC Garganese, F Torroni, A Pane, G Federici di Abriola, G Ciofetta**

Digestive Surgical and Endoscopic Unit - *Nuclear Medicine Unit, "Bambino Gesù" Children's Hospital IRCCS, Rome, Italy

Purpose. To report our scintigraphic, endoscopic and surgical data before and after Nissen fundoplication (NF) in children with gastroesophageal reflux disease (GERD) and delayed gastric emptying (DGE) to determine the efficacy of pyloromyotomy (P) in gastric emptying (GE) normalization.

Methods. From January 2002, 52 children (30 male; 10 esophageal atresia (A/E) and 3 congenital diaphragmatic hernia; mean age 14 years -range 4 months/23 years), with severe GERD, without neurological disorders, were studied. Before and one year after NF, endoscopy and scintigraphy were performed. Scintigraphy used a ^{99m}Tc -DTPA labeled liquid and solid meal. GE% in 60' was measured. GE differences at baseline and at follow up were estimated by the student's t test. In presence of DGE, P was associated to NF.

Results. No intra/post-operative complications occurred. The baseline scintigraphy identified two groups of pts: I) 28pts with normal GE (mean GE%=57.78), underwent to NF alone; II) 24pts with DGE (mean GE%=18.04), considered for NF+P. GE% difference was striking ($t=10.296$; $p<0.001$). At follow up, GE% was increased in both groups. In the 1st group mean post-operative GE% was 60.35% but its variation is not statistically significant ($t=0.552$; $p=0.583$). In the NF+P group, mean GE% increased to 53.34 ($t=7.891$; $p<0.001$) with normalization of the preoperative data. Two patients with E/A, operated on N+P at 4 months of life for ALTE, had recurrent GERD. Two children presented transient dysphagia.

Conclusions. P is a safe and efficacious procedure for GE normalization in patients with DGE. Before surgery, all patients with GERD should be evaluated by scintigraphy.

P6

MECHANISMS OF POSTOPERATIVE DYSMOTILITY IN THE SMALL INTESTINE ASSOCIATED WITH INTERSTITIAL CELLS OF CAJAL AND PROTECTIVE EFFECTS OF INDUCIBLE NITRIC OXIDE INHIBITION

H. Yanagida¹, K. M. Sanders² and S. M. Ward²

¹Division of Neuroscience, JCSMR, The Australian National University, Canberra, Australia, ²Department of Physiology and Cell Biology, University of Nevada, Reno, Nevada, USA

We have previously shown that surgical manipulation of the intestine causes disruptions in electrical activity and in the associated networks of interstitial cells of Cajal (ICC) as observed 5-hours after surgery, and that these disruptions contribute to post-operative dysmotility. In this study we examined the effect of inhibition of inflammatory pathways using inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) on the murine surgery model. 2cm segments of ileum were resected and the intestine was reconstructed in control, iNOS inhibitor (aminoguanidine, 1400W) pretreated and knockout (iNOS^{-/-}, COX-2^{-/-}) mice. 5-hours after surgery, the intestines were examined using Kit-immunohistochemistry and intracellular recordings. In control mice, the electrical activity was reduced in amplitude and the ICC network was disrupted 5-hours after surgery in a distance dependent manner. Compared to control mice, COX-2^{-/-} mice showed greater slow wave amplitudes and greater populations of ICC. The electrical activity and ICC networks in iNOS^{-/-} mice remained normal ($P>0.05$, compared to sham-operated mice) at 1-5cm from the resection site, as was the case for preoperatively iNOS inhibitor treated mice. Postoperative dysmotility is associated with acute loss of electrical activity and loss of ICC networks 5-hours after surgery. iNOS inhibition, more effectively than COX-2 inhibition, during surgery may reduce postoperative dysmotility and may offer the advantage of quick recovery from dysmotility.



CAPSULE ENDOSCOPY AND NON-HAEMORRAGIC SMALL BOWEL DISEASES: PRELIMINARY RESULTS

F Bonfante, M Tebaldi, S Pistoso and W Piubello

Department of Internal Medicine and Endoscopic Unit,
Hospital of Desenzano del Garda, Brescia, Italy

Introduction. The study of the small bowel diseases is the first indication for wireless capsule endoscopy. Occult gastrointestinal bleeding or sideropenic anemia with negative conventional endoscopic and radiological methods are the main indications, but even patients with suspected malabsorption, celiac disease with symptoms in gluten free diet or patients with suspected Crohn's disease are good candidates for capsule endoscopy because finding lesions may lead to a diagnosis or treatment change.

Aim. To evaluate the effectiveness of the capsule endoscopy in the study of suspected small bowel disease in patients with negative upper and lower endoscopy and small bowel follow through.

Patients and Methods. From December '03 to June '05, 14 patients (8 men, mean age 47,2, range 29-74) went to our attention for capsule endoscopy: three patients suffered for celiac disease non responsive to gluten free diet, two patients were affected by malabsorption syndrome (diarrhoea, weight loss) and the other were investigated for suspected Crohn's disease. The exploration was performed after intestinal preparation and eight-hour fasting; all exams were well tolerated and no non-natural excretion occurred.

Results. Capsule endoscopy was normal in 6/14 patients (42%) and pathological in 8/14 patients (58%). All patients with celiac disease reported ulcerative jejunum-ileitis compatible with refractory disease; the same endoscopic pattern was seen in one patient with malabsorption; in four patients with suspected Crohn's disease, we found erosions and intestinal ulcers suggestive of IBD pathology.

Conclusions. Capsule endoscopy is effective in the diagnostic of small bowel non haemorrhagic diseases in patients with inconclusive traditional endoscopic and radiological evaluation.



EFFICIENCY OF ADDING 6 MERCAPTOPYRINE (6 MP) IN CORTICODEPENDENT ULCERATIVE COLITIS AND EFFICIENCY OF INFLIXIMAB (INFL) IN REFRACTORY ULCERATIVE COLITIS (UC)

D Olteanu, D Lupu, M Abbas

Internal Medicine I, University Hospital, Bucharest, Romania

Patients and Methods. From 130 patients with moderate or severe corticoid dependent UC, 110 patients received 6-MP and 20 patients were maintained on corticoid monotherapy. These patients were observed for 120 days. Those who obtained a remission were observed further for 180 days.

Patients who did not respond to corticotherapy and 6-MP received Infliximab (INFL) 5 mg/kg (50% of patients) and INFL 10 mg/kg (50% of patients) in week 1, 3, 7 and then every 8 weeks, for 40 weeks.

Results. From 110 patients treated by adding 6-MP to corticotherapy we obtained a persistent remission in 60% (46 patients). Among these 46 patients, 10 patients didn't tolerate azathioprine but tolerated well 6-MP. Among those maintained on corticotherapy alone, only in 10% (2 patients) a persistent remission was obtained. In 64 patients refractory to 6-MP added to corticotherapy INFL was added. In those who received INFL 5mg/kg (32 patients) we obtained a clinical remission at week 8 in 38% and at week 30 in 45% and an endoscopic mucosal remission in 48% of patient at week 30. In those who received INFL 10 mg/kg (32 patients) we obtained a clinical remission in 34% at week 8 and in 58% at week 30 and an endoscopic remission in 60% of patients at week 30.

Conclusions.

- 1) Adding 6-MP to corticotherapy increases the rate of persistent remission in corticoid dependent UC.
- 2) Infliximab increases the rate of clinical and endoscopic remission in over 40% of cases at dose of 5mg/kg and over 50% of cases at dose of 10 mg/kg administrated in week 1,3,7 and then in every 8 week for 40 weeks.

SMAD3-KNOCKOUT MICE LACK INTERSTITIAL CELLS OF CAJAL IN THE COLONIC WALL

G Latella¹, A Vetuschì², R Sferra², A D'Angelo¹, V Catitti¹,
G Zanninelli¹, M Chiaramonte¹, R Caprilli³, E Gaudio⁴

¹Cattedra di Gastroenterologia, Università degli Studi di L'Aquila, Italy; ²Cattedra di Anatomia Umana, Università degli Studi di L'Aquila, Italy; ³Cattedra di Gastroenterologia I, Università degli Studi di Roma "La Sapienza", Italy; ⁴Cattedra di Anatomia Umana, Università degli Studi di Roma "La Sapienza", Italy

Background & Aim. Transforming growth factor- β (TGF β)/Smads signaling pathway plays a pivotal role in organogenesis, oncogenesis, inflammation, repair and fibrosis. The aim of this study was to evaluate the morphology of muscle layers and the density and distribution of interstitial cells of Cajal (ICC) in the colon of Smad3 knockout mice.

Materials and Methods. Eighteen Smad3 wild-type and twelve null mice were sacrificed at 4 months of age and the colon was collected for histology (Hematoxylin-Eosin, Masson trichrome, Gomori silver staining), morphometry and immunohistochemistry (IHC) analysis. For IHC were used c-kit, α -smooth muscle actin (α -SMA), vimentin, desmin, and neuronal cocktail (S-100, NSE, neurofilament 200) antibodies.

Results. When sacrificed, 40% of the null mice showed different degrees of colon dilatation, compared to wild-type. Histological and morphometric evaluation revealed a significant reduction in muscle layer thickness of the colon in all the null mice as compared to wild-type. Immunohistochemistry evaluation showed a marked reduction or even absence of c-kit immunoreactivity, which identifies ICC, in the colon of all the null mice, compared to wild type.

Conclusions. Smad3 null mice show a marked reduction or even absence of ICC in the colon together with a concomitant reduction of intestinal smooth muscle layer thickness. This data could account for the colonic dilation observed in about 40% of Smad3 null mice. The results of the study suggest that TGF β /Smad3 signaling pathway play an important role in the development and differentiation of intestinal smooth muscle cells and ICC. Loss or damage of ICC network is involved in a variety of intestinal motility disorders.



COLONIC MUSCLE CELL DAMAGE INDUCED BY EXPOSURE OF HUMAN MUCOSA TO A PATHOGENIC LIPOPOLYSACCHARIDE IS MEDIATED BY OXIDATIVE STRESS AND BY PROSTAGLANDINS

M Guarino¹, S Carotti¹, C Severi², G Di Cuonzo³, I Tattoli²,
R Alloni¹, AM Altomare¹, M Cicala¹

¹Department of Digestive Diseases of Campus Biomedico University,

²Department of Clinical Sciences, University La Sapienza,

³Department of Laboratory Medicine, Campus Biomedico University, Rome, Italy

The suppression of intestinal muscle contractility induced by lipopolysaccharide (LPS) in animal models of septic ileus has been suggested to be mediated by acute activation of macrophages which primarily release inflammatory mediators and reactive oxygen species. Suppression of colonic smooth muscle cell (SMC) contractility induced by inflammation and oxidative stress seems to be mediated by the activation of the transcription factor NF-kappa B. **Aim.** To define if human mucosal exposure to LPS is related to oxidative stress and whether this leads to suppression of muscle cell contractility via activated NF-kappa B and prostaglandin release. **Methods.** From fresh specimens of human colon, the mucosa and submucosa were removed and sealed between two chambers, with the luminal side of mucosa facing upward and covered with 5mL of Krebs solution, and the submucosal side facing downward into 20mL of Krebs. Both chambers were oxygenated and kept at 37°C. LPS (Sigma) obtained from the pathogenic strain of Escherichia coli 0111:B4 was added to the luminal side of the mucosa and kept for 30 minutes. Enzymatically isolated SMCs were exposed for 30 minutes to normal buffer or to buffer from the submucosal chamber of mucosa pre-exposed to LPS (LPS-buffer). SMCs were incubated for 15 minutes with LPS-buffer in the absence or presence of H₂O₂ scavenger catalase (1,200U/mL) or indomethacin (5 η M), a cyclooxygenase inhibitor. Furthermore SMCs were pre-incubated with MG132 (0.1 η M, for 15 min), an inhibitor of NF-kappa B activation, before direct LPS exposure (50ng/mL). At the end of pre-incubation periods acetylcholine (ACh) (10-6M) contraction-response was tested.

Results. SMCs incubated with normal buffer showed a maximal contraction of 26 \pm 2%. SMCs exposed to LPS-buffer presented no change in the resting cell length (5.5 \pm 2% decrease of unstimulated cell) but inhibition of maximal contraction of 75.3 \pm 6% compared to response in normal buffer. The inhibition was reversed by preincubation of SMCs with either indomethacin or catalase (18.5 \pm 5% and 7.8 \pm 2% inhibition of maximal contraction, respectively). Inhibition of maximal contraction was also reversed in cells pretreated with MG132, before direct LPS exposure (11.2 \pm 3%). **Conclusions.** The relevant impairment of SMC contractile response, observed after acute exposure of colonic mucosa to a pathogenic LPS, is reversed by the inhibition of cyclooxygenase expression and NF-kappa B activation and by removing H₂O₂. It is conceivable that excessive mucosal and/or muscular oxidative stress triggers an increased production of prostaglandins which leads to suppression of muscle cell contractility via NF-kappa B activation.



PATIENTS WITH CLINICALLY DIFFERENT SYMPTOM-BASED DIAGNOSIS OF FUNCTIONAL BOWEL DISORDERS MAY HAVE IDENTICAL SPECIFIC AND NON SPECIFIC ILEO-COLO-RECTAL MICROSCOPIC ABNORMALITIES

A Marcheggiano¹, A Covotta², C Iannoni¹, D Badiali¹, R Cantarini¹, M Paoletti², N Pallotta¹, E Corazziari¹

¹Department Scienze Cliniche, University "La Sapienza", Rome, Italy. ²Department of Surgical Sciences, University "La Sapienza", Rome, Italy

Patients with endoscopy negative symptom-based diagnosis of functional bowel disorders (BD) may present specific and non-specific microscopic abnormalities that can affect the mucosa of one or more sites of the large bowel and terminal ileum. **Aim** of this study was to evaluate whether the clinical presentation of the BD differs according to the site affected by, and the specific or non-specific type of, the microscopic abnormality. **Methods.** Thirty-four consecutive patients (22 F; age range 22-70 yrs), with normal serum biochemistry, CBC, thyroid function, EMA, and normal ileum-colonoscopy were evaluated. Sixteen patients matched the symptom-based diagnosis of IBS, five of functional diarrhea (FD), and thirteen of unspecified functional bowel disorders (UFBD). Biopsies of the terminal ileum (n=2) cecum (n=1), ascending (n=1), transverse (n=1), descending (n=1), sigmoid (n=1) colon, and rectum (n=1) were stained with H-E for microscopic assessment by a pathologist unaware of the clinical diagnosis. **Results.** Histological abnormalities were found in 9 (26.5%) patients: 3 IBS, 2 functional diarrhea and 4 UFBD. Increased lymphoplasmacytic infiltrate and granulocyte clusters were present at the level of a) the ileum only in 1 IBS patient, and in 2 UFBD patients; b) the cecum only in 1 IBS patient. Altered crypt architecture was present in the rectum only in 1 UFBD. Collagenous colitis was present in 1 IBS, 2 functional diarrhea, and 1 UFBD, patients. **Conclusions.** Non-specific microscopic abnormalities of the ileo-colonic-rectal mucosa and specific microscopic collagenous colitis may be equally present in patients with different clinical presentation of symptom-based diagnosis of functional bowel disorders.

P15

RISK FACTORS OF IRRITABLE BOWEL SYNDROME (IBS) - LIKE SYMPTOMS IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE (IBD)

C Fierbinteanu-Braticevici¹, L Tribus¹, P Dragomir¹, T Badescu², D Andronescu¹

¹Medical Clinic II, Department of Gastroenterology, University Hospital Bucharest, Romania ²Medical Clinic, Department of Gastroenterology, Bucharest, Romania

Background. Functional symptoms, particularly pain and diarrhea are common in patients with proven IBD without signs of inflammation relapse, which may cause mismanagement.

Aim. To assess the prevalence of IBS-like symptoms in patients with IBD in remission and to investigate the predictive factors for IBS occurrence in these patients.

Methods. 42 patients with proven remissive IBD: 25 ulcerative colitis (UC) and 17 Crohn's disease (CD) were studied. The patients were matched for disease duration and use of medication. All the patients underwent clinical, biological, ultrasonographic and endoscopic evaluation. IBS symptoms were scored using the Roma II criteria. Quality of life was assessed through a mailed questionnaire.

Results. The prevalence of IBS-like symptoms was 31% in UC and 45% in CD. Multivariate analyses showed that the following parameters: sex (female - 62%), psychiatric comorbidity (major depression, anxiety and somatoform disorders -40%) and other disorders: fibromyalgia (31%), chronic fatigue syndrome (53%) and chronic pelvic pain (38%) were associated with the onset of IBS-like symptoms. The extent of colitis and the duration of IBD did not predict IBS onset.

Conclusions. IBS-like symptoms occurred in over one third of IBD remissive patients. Female sex and psychiatric comorbidity are predictors for IBS occurrence and improve the selection of IBD patients for serotonergic agents added to the specific IBD therapy.

P8

ULTRASOUND EVALUATION IN DIAGNOSIS AND FOLLOW-UP OF ACUTE COLONIC DIVERTICULITIS

C Fierbinteanu-Braticevici, L Negreanu, A Bengus, R Usvat, D Andronescu
Medical Clinic II, Department of Gastroenterology, University Hospital, Bucharest, Romania

Background. The diverticular disease affects approximately 10% of population over 45 years old and almost 80% of those over 85. Acute diverticulitis remains a common clinical problem encountered in 20% of patients with diverticular disease.

Aim. To evaluate the role of abdominal ultrasound in the diagnosis and follow-up of inflammatory diverticular disease.

Methods. 40 patients with abdominal symptoms were diagnosed by CT with acute diverticulitis and were evaluated by ultrasonography during the evolution of the disease. All were treated with a combination of Ciprofloxacin and Metronidazol for ten days. The echographic results were compared with CT assessments.

Results. 37 patients (93%) had positive findings of acute diverticulitis at ultrasonography. These include: hypoechoic cockade protruding from the colonic wall, thickened colonic wall, pain on compression of the affected region, central hyperechoic lumen (air/feces in diverticulitis) and increased echogenity around the diseased colon (pericolitis). Three patients underwent ultrasound guided aspiration of the sigmoid abscess. Five patients required surgery: three for perforation (ultrasound-free fluid and air in portal system) and two for fistula formation (sigmoidovesical). Only three (7%) diagnosed on CT with acute diverticulitis had no ultrasound findings.

Conclusions. Ultrasound is the imaging method of choice for primary diagnosis of acute diverticulitis and for follow-up. This procedure is helpful in deciding on conservative treatment or surgical intervention.

P9

SYMPTOMATIC CHARACTERIZATION OF UNCOMPLICATED COLON DIVERTICULAR DISEASE

F De Giorgi, F Baccini°, G Maconi#, A Rispo\$, L Pasquale\$, G Sarnelli*, B Annibale°, R Cuomo**

*Gastroenterologia, Dipartimento Medicina Clinica e Sperimentale, AOU Federico II Napoli, Italy; °Dipartimento di Malattie Digestive, Ospedale S.Andrea, Università La Sapienza, Roma, Italy; #Dipartimento di Gastroenterologia, Ospedale Universitario L.Sacco, Milano, Italy; \$U.O. di Gastroenterologia, ASL AV1, P.O. Ariano Irpino, Avellino, Italy

The impact of upper and lower gastrointestinal symptoms in uncomplicated diverticular disease (DD) is not well documented, as well as the overlap with irritable bowel syndrome (IBS) and functional dyspepsia (FD). Our aim is to evaluate in DD the comorbidity with IBS and FD. **Methods.** 74 patients (30 m; 47-76 years), with x-ray diagnosis of diverticulosis were recruited from 4 gastroenterological centres. Symptoms like recurrent abdominal pain <24 hours, painful episodes >24 hours (clue of undiagnosed diverticulitis), bloating and alterations of defecation were collected. Dyspeptic symptoms (fullness, nausea, vomiting, early satiety, epigastric burning and pain, belching) and IBS Rome II criteria were also evaluated. SF-36 v2 health questionnaire was used to quantify the impact on quality of life. **Results.** Recurrent short-lived abdominal pain (<24h) and bloating were present in 78% of patients, while 21% reported prolonged painful episodes (>24h). 46 patients (62%) meet the IBS Rome II criteria, classified as constipation and diarrhoea-predominant-IBS in 32 and 30% of cases respectively. Dyspepsia, defined as the presence of two or more dyspeptic symptoms scored as relevant or severe, was present in 47 patients (64%) and the most prevalent symptoms were fullness (44%) and belching (50%). In 40 patients (54%) we found an overlap between IBS and dyspepsia. All patients had low rates of mental component scores on SF-36 scales. **Conclusions.** IBS and dyspepsia represent a great part of clinical presentation in DD. As mental component impairment is typically recorded in IBS and dyspepsia our findings confirm that functional disorders are involved in symptoms complaining of DD.

P10

RECTOCELE AND INTRARECTAL/ANAL INTUSSUSCEPTION ARE NOT RELATED WITH IMPAIRED RECTAL TRANSIT AND EMPTYING IN FUNCTIONAL CONSTIPATION

F Alghisi, D Badiali, R Cappuccio, F Anzini, E Corazziari, FI Habib
Department Clinical Sciences, University "La Sapienza", Rome, Italy

Rectocele and intra-rectal/anal intussusception are frequent findings in chronic constipation, and their surgical repair has been proposed for the treatment of obstructed defecation syndrome. However, it is not established whether rectocele and intra-rectal/anal intussusception, per se, affect rectal transit and/or emptying. Aim of this study was to assess the relationship between rectocele and intra-rectal/anal intussusception with rectal transit and/or emptying. **Materials and Methods.** 146 consecutive patients (F 130, mean age 45.8 ± 13.6 yrs), affected by functional chronic constipation according to ROME II criteria, were submitted to defecography and measurement of rectal transit time by means of radio-opaque markers assessed at 72-hrs intervals on abdominal antero-posterior x-ray. To identify the rectum, a latero-lateral radiogram, including sacrum and coccyx, was added when markers reached the pelvis. At defecography the presence of significant rectocele (>3.5 cm), intra-rectal/anal intussusception, and post-evacuative residue were assessed. **Results.** Rectal transit was delayed in 45 pts (30.8%). The following defecographic findings were found: rectocele 32.2%, intra-rectal/anal intussusception 41.8%. The frequency of prolonged rectal transit did not differ in patients with, and without, rectocele ($\chi^2=0.12$, n.s.) and intra-rectal/anal intussusception ($\chi^2=0.01$, n.s.). A moderate/severe post-evacuative residue was observed in 66.4% of the patients, with no statistical difference between patients with and without defecographic changes or delayed rectal transit. **Conclusions.** The results of this study suggest that both rectocele and intra-rectal/anal intussusception, per se, scarcely affect rectal emptying and do not delay transit through the rectum.

P11

HISTOCHEMISTRY IN HIRSCHSPRUNG'S DISEASE: THE NEW ERA OF DIAGNOSTIC KITS

G Martucciello¹, F Venerucci², C Sbona²

¹IRCCS Policlinico "S. Matteo", Pavia; Italy; ²Bio-Optica, Milan, Italy

Background. Hirschsprung's Disease (HD) is a neurocristopathy that occurs in approximately 1 per 5000 newborns worldwide. It is characterized by the congenital absence of ganglion cells in the rectum and distal colon resulting in a functional obstruction, which manifests as severe constipation.

Methods. Diagnosis is performed on rectal suction biopsy specimens taken 2 to 10 cm above the pectinate line. Acetylcholinesterase (AChE), Lactic Dehydrogenase (LDH), and NADPH-diaphorase (NADPH-d) histochemical techniques were performed on serial cryostatic sections (1).

The most common complications of HD are related to problems of misdiagnosis. These are:

- False positive diagnosis in Pseudo-HD
- False negative diagnosis in true HD with risk of occlusion, enterocolitis and death
- Non-radical treatment of persistent aganglionosis
- Too radical treatment with the risk of extensive resection of a long segment of normoganglionic intestine

The gold-standard techniques for this pathology are:

- AChE: to assess the infiltration of cholinergic fibers into the lamina propria of the gut, the criterion for HD, in pre-operative mucosal biopsies; and the
- ANE technique: useful for intraoperative examination to determine the degree of anastomosis, where the ganglion cells begin to appear.

It is often very difficult to prepare the incubation medium within a limited time in pathology laboratories.

Results and Conclusions. The authors present a new enzymo-histochemical diagnosis kit for pathologist and gastroenterologists, produced by lyophilization. The kit, which is ready for use, can easily be used at room temperature or stored at $+4^{\circ}\text{C}$ for several months. Produced by Bio-Optica, Milan, the kit contains lyophilized AChE and ANE reagents for preoperative diagnosis and for intraoperative examinations on cryostatic sections.

Succinic Dehydrogenase and NADPH-diaphorase will also be added to the kit in 2006.

References

1. Meier-Ruge WA, Bruder E. *Pathology of Chronic Constipation in Pediatric and Adult Coloproctology*. Karger 2005
2. Martucciello G, Pini Prato A, Puri P, et al. *Controversies concerning diagnostic guidelines for anomalies of the enteric nervous system: A report from the fourth International Symposium on Hirschsprung's disease and related neurocristopathies*. J Pediatr Surg 2005;40:1527-1531



A NEW MINI-INVASIVE TECHNIQUE TO OBTAIN FULL-THICKNESS COLON BIOPSIES VIA ONE-TROCAR TRANSUBILICAL LAPAROSCOPY FOR DIAGNOSIS OF COMPLEX ENTERIC NERVOUS SYSTEM ABNORMALITIES

G Martucciello, P Romano

Department Paediatric Surgery IRCCS Policlinico "San Matteo" Pavia, Italy

Background. Hirschsprung's disease (HD, Congenital Aganglionic Megacolon) is the most common (1:5000 live births) ENS anomaly. However, other conditions like Hypoganglionosis, Intestinal Neuronal Dysplasia (IND) and Colonic Desmosis can cause severe chronic constipation and motility disorders of the gut. While the international protocol for the diagnosis of HD starts from suction rectal biopsies using Acetylcholinesterase enzyme histochemical reaction staining (Bio-Optica diagnostic Kit, Milan), the diagnosis of other complex ENS abnormalities could require full-thickness intestinal biopsies and other specific histochemical investigations.

Methods. The authors present a new mini-invasive surgical approach aimed at obtaining one-trocar transumbilical full-thickness laparoscopic intestinal biopsies for sharp diagnosis of any ENS abnormality. Patients received preoperative antibiotic prophylaxis and bowel preparation. Under general anaesthesia the periumbilical region was infiltrated with bupivacaine. The operation was performed through one infra-umbilical sagittal incision with an 11 mm port inserted by the Hasson technique. Pneumoperitoneum was established at 8 to 12 mm Hg (according to the age of the patient). A 10-mm operating telescope (Karl Storz operative canal) was used, with a 5 mm atraumatic grasper introduced through the operative channel. Using one-trocar transumbilical laparoscopic exploration, it was possible to identify the different intestinal segments to study and pull critical regions outside the abdominal cavity through the umbilical incision. This is the best technique to obtain several full-thickness biopsies without peritoneal contamination.

Results. The authors performed this procedure in 5 selected patients, obtaining biopsies from the sigmoid colon, the descending colon, the transverse colon and the ascending colon. The histochemical studies of these biopsies allowed the diagnosis of intestinal hypoganglionosis of the myenteric plexus in 4 cases and diffuse IND in one case of chronic pseudo-obstruction. We had no post-operative complications.

Conclusions. Our results indicate that this technique, which combines the advantages of the open and the laparoscopic procedures, is the best approach to study selected, very complex cases of ENS disorders.



DO RADIO OPAQUE TRANSIT STUDIES PREDICT QUALITY OF LIFE IN PATIENTS WITH CHRONIC CONSTIPATION?

S Cowlam¹, D Wooff², I Minty¹, S Green¹, J Varma¹, Y Yiannakou¹

¹University Hospital of North Durham, Durham, UK

²Statistics & Mathematics Unit University of North Durham, UK

Introduction. Transit marker studies are commonly used to assess severity in chronic constipation but have not been validated for this purpose.

Aim. To determine whether results of transit studies correlate with QOL measurements obtained using validated QOL instruments.

Methods. 110 out of 163 consecutive patients referred to a dedicated constipation clinic completed evaluations of QOL and colonic transit before therapy. Patients met Rome II criteria for idiopathic constipation. Median age 40.5 years, 96% of patients were female. Median symptom duration; 10.5 years. The Gastrointestinal Quality of Life Index (GIQLI) and Patient Assessment of Constipation – Quality of Life (PAC-QOL) were completed by the patients. A high GIQOLI suggests better QOL. A high PAC-QOL suggests poorer QOL. Transit studies performed using recognised protocols with Sitzmarks (Konsyl). Segmental marker counts expressed as TSM-out (number of markers passed at day four) and TSM-centre (average marker position). Analysis using Pearson correlation coefficient.

Results. There was no correlation between transit study results and QOL assessments. Correlation coefficients: TSM-centre vs GIQLI, -0.057; TSM-centre vs PAC-QOL, -0.036; TSM-out vs GIQLI, 0.034; TSM-out vs PAC-QOL 0.092. There was good correlation between GIQLI and PAC-QOL, -0.562 ($p < 0.001$). Correlations between other pairs were effectively not different to zero.

Conclusion. Transit study results in chronic constipation did not predict quality of life. We have previously shown that they do not correlate with symptoms either. It is unlikely that they could be used to assess the severity of constipation. They may still have a role to confirm the diagnosis of constipation.



PHENOTYPIC VARIATION IN DISORDERS OF DEFECATION IN SPINAL CORD INJURED PATIENTS

G Bazzocchi, PF Almerigi, E Poletti, P Pillastrini, M Menarini
Montecatone Rehabilitation Institute S.p.A., University of Bologna
Bologna, Italy

During 2004, 75 consecutive patients (57 males, 42 paraplegic, 33 tetraplegic, mean age 46 years, range 19-76 years) reporting unsatisfactory bowel habit in spite of the therapy with laxative, suppositories and/or enema, were evaluated by means of Rome II Diagnostic Criteria for Intestinal Functional Disorders. Patients with injury since < 6 months, conus or cauda lesions, cerebral lesions and g.i. disorders preceding neurological lesion were excluded. Complete proctologic examination, anorectal manometry and Intestinal Transit Study were performed. Four types of bowel disorders were recognized: (A) obstructed defecation due to structural abnormalities such as rectal prolapse, intussusception or rectocele; (B) colonic dysfunction with delayed total and/or segmental transit and abnormal rectal filling; (C) difficult defecation with evidence for incomplete evacuation and/or time >1 hour for rectal emptying; (D) fecal incontinence and/or anal soling. No relationship between the four disorders of defecation with type, level of the injury, ASIA scores and characteristics of bladder disorder was found. In the 44.5% of the female versus the 24% of males ($p=0.02$, Fisher's Exact Test) the pathophysiologic mechanism underlying the intestinal disorder was not related to the neurological damage *per se*. The present study shows that: 1) constipation and fecal incontinence are not exhaustive for describing "neurogenic bowel" clinical pictures; 2) differently from bladder disorders, further factors other than spinal cord injury seem to play a role in the occurrence of bowel dysfunction.

P12

EFFECT OF A NEW TRANS ANAL IRRIGATION METHOD ON COLONIC CLEARING OF RADIOOPAQUE MARKERS IN PATIENTS WITH SEVERE CONSTIPATION

G Bazzocchi, PF Almerigi, E Poletti, P Pillastrini, M Menarini
Montecatone Rehabilitation Institute S.p.A., University of Bologna
Bologna, Italy

Background. Retrograde colonic irrigation is beneficial for defecation disturbances (Colorectal Disease 2004; 6:185-90). Scintigraphic study showed that colonic emptying obtained by retrograde colonic washout was greater than that by normal defecation (Dis Colon Rectum 2003; 46: 68-76). Aim of the present study was to evaluate the decrease in number of radioopaque markers in the colonic segments after a unique session of colonic washout (TAI) performed by a device equipped with a new enema continence catheter (Peristeen® by Coloplast - Denmark) fit for an 800 ml infusion of tap water in 8 min allowed by a constant positive pressure inside the system.

Methods. Sixteen patients (14 females, mean age 42.5 yrs, range 32-64) fulfilling the Rome II Criteria for Functional Constipation were evaluated according to the Abrahamsson's technique for the Intestinal Transit Time Study: a single abdominal x-ray after 10 marker daily ingestion for six days. Then, TAI session was performed and a second x-ray was obtained immediately following patient evacuation.

Results. Mean Total Transit Time was 5.83 days (range 5.1 - 6.5 days): 21(6), 20.6(5.4) and 11.5(3.4) markers were present in the right colon, left colon and in the recto-sigmoid tract respectively. After TAI-induced defecation, a statistical significant decrease (T-test for paired data) in the retained markers was observed: 8.2(4), 8(2.7) and 4(4.3) in the three colonic segments respectively ($p<0.02$).

Conclusions. Retrograde colonic irrigation by means of Peristeen® is effective for inducing colonic emptying also of the ascending and transverse colon in constipated patients with very slow transit.

P13

MEDICAL TREATMENT OF ENCOPIRESIS IN CONSTIPATED CHILDREN

F Bracci, D Badiali, F Anzini, E Corazziari
Department of Clinical Sciences, University "La Sapienza"
Rome, Italy

Encopresis is the involuntary loss of stool into the child's underwear in the presence of functional constipation; it is reported to affect 1.5-2.8% of children (Loening-Baucke, 1993). The suggested treatment is based on enemas and/or low pediatric doses of oral laxatives, either alone or associated with psychotherapy. However it is not known whether an aggressive medical approach, without psychotherapy, is effective in the treatment of encopresis in constipated children.

Aim. This study evaluated the effectiveness of treatment with enemas associated with high oral dose of an osmotic laxative (lactitol), sustained by a regular follow up, at short time intervals.

Methods. Twenty-four consecutive encopretic children (M=19; mean age=11.5±3.1 years) with evidence of fecal impaction at rectal examination, were included in the study. All patients were treated with cleansing enemas (3/week during first 2 weeks) and oral administration of lactitol (>40g/24hrs) to obtain satisfactory defecation of soft stools. The patients did not undergo psychotherapy, but they were controlled fortnightly to assess rectal impaction, reinforce collaboration of the children and of their families, modify dose of laxatives and/or enemas according to episodes of encopresis, presence of rectal impaction, frequency and consistency of stools. The endpoint of treatment was considered complete absence of encopresis.

Results. Mean age at the onset of encopresis was 6.3±2.8 years; at least one episode daily of encopresis was reported by all children; mean duration of encopresis was 5.4±4.3 years. Encopresis disappeared in 20/24 (83%) children. The mean dose of lactitol required was 60±20mg/daily and mean duration of therapy until disappearance of encopresis was 9.1 ±9.4 weeks. Children aged less or more than 12 years did not differ for lactitol dose (59±17 vs 60±25), and resolution period (12.3±3.5 vs 11.6±10.9 weeks).

Conclusion. Rectal dysimpaction by means of enemas in association with daily high doses of lactitol seems to be effective in the treatment of encopresis in constipated children, independently from psychotherapy.



CHRONIC CONSTIPATION: RESULTS OF A CLINICAL OBSERVATION IN THE USE OF FR.E.M.S. (FRequency modulated ElectroMagnetic neural Stimulation) THERAPY. PILOT STUDY

M Massari°, A Zanella**, P Desideri °, G Rando*, A Wiel Marin*.*
*Department of Surgical Sciences, U.O.C. General Surgery 1, Catholic University S. Heart-Columbus Hospital Rome, Rome, Italy; **Lorenz Biotech, Medolla, Modena; °Ce.Te.Ri. Rehabilitation Therapy Centres, Onlus, Rome, Italy

Introduction. The motility function, immune modulation, enteric sensibility, permeability of the mucosal and the submucosal vascular system, proliferation and activities of the enterochromaffin cells, are subject to semiautonomous control of the ENS and his interactions with CNS, via the autonomous nervous system through electrical signals, generated by transmembrane action potentials. **Aim.** Our pilot study consists of a clinical evaluation of the effects on the colonic motility of a transcutaneous negative, asymmetrical, electrical pulse patterns administration. **Materials and methods.** Selected 15 patients with chronic constipation, excluding the presence of IBD, outflow dysfunction or defecatory disorders, underwent to cycle of transcutaneous 15 daily pulsate current FR.E.M.S. therapy, at fixed and variable frequency (software controlled). The electromagnetic fields have been administered using two methods: on ascending, transverse and descending colon segments, with fixed frequency (400 Hz, 30-40 seconds, 70-250 Volts, patient controlled through remote control), on the sigmoid tract with variable frequency (1-100 Hz, 10-90 seconds, 70-250 Volts, patient controlled). **Results.** On all patients we obtained spontaneous bowel habit regularization, daily, 3 b.m./week (6 cases), 2 b.m./week (8 cases). In one case a second therapy cycle to obtain spontaneous tri-weekly evacuations was necessary. The 12 months follow-up, showed the persistence of bowel habit results for 6-8 months without need of chologogues. **Conclusions.** We hypothesize that FR.E.M.S. therapy may interact with the neuronal systems (brain-gut axis) through an electrophysiological stimulation. Our next step consists of a development of a protocol aimed to investigate the immunohistochemical and biochemical modifications induced by electromagnetic fields generated by this type of pulse.

Author Index

- *Lectures and Abstracts*

Author Index

	<i>Page</i>		<i>Page</i>
<i>Abbas M</i>	72	<i>Caprilli R</i>	73
<i>Alghisi F</i>	76	<i>Carotti S</i>	73
<i>Alloni R</i>	73	<i>Catitti V</i>	73
<i>Almerigi PF</i>	78	<i>Chan Y-M</i>	70
<i>Altomare AM</i>	73	<i>Chiaramonte M</i>	73
<i>Altomare DF</i>	52	<i>Cicala M</i>	73
<i>Andronescu D</i>	74, 75	<i>Ciofetta G</i>	71
<i>Annibale B</i>	75	<i>Collins SM</i>	36
<i>Anzini F</i>	76, 79	<i>Corazza GR</i>	31
<i>Auricchio S</i>	45	<i>Corazziari E</i>	19, 74, 76, 79
<i>Azpiroz F</i>	27	<i>Corsetti M</i>	40
<i>Baccini F</i>	75	<i>Covotta A</i>	74
<i>Badescu T</i>	74	<i>Cowlam S</i>	77
<i>Badiali D</i>	48, 74, 76, 79	<i>Cuomo R</i>	75
<i>Basilisco G</i>	37	<i>Dall'Oglio L</i>	71
<i>Bassotti G</i>	70	<i>D'Angelo A</i>	73
<i>Battaglia E</i>	70	<i>De Angelis P</i>	71
<i>Bazzocchi G</i>	42, 78	<i>De Carne M</i>	69
<i>Bengus A</i>	75	<i>De Giorgi F</i>	75
<i>Bonfante F</i>	72	<i>De Ponti F</i>	57
<i>Bracci F</i>	79	<i>Delvaux MM</i>	25
<i>Bueno L</i>	59	<i>Desideri P</i>	79
<i>Caldaro T</i>	71	<i>Di Cuonzo G</i>	73
<i>Campieri M</i>	42	<i>Di Lorenzo C</i>	32
<i>Cantarini R</i>	74	<i>Di Stefano M</i>	31
<i>Cappuccio R</i>	76	<i>Dragomir P</i>	74

Author Index

	<i>Page</i>		<i>Page</i>
<i>Drossman DA</i>	29	<i>Lupu D</i>	72
<i>Dughera L</i>	70	<i>Maconi G</i>	75
<i>Emanuelli G</i>	70	<i>Malagelada J-R</i>	28
<i>Farthing MJG</i>	38	<i>Marcheggiano A</i>	74
<i>Federici di Abriola G</i>	71	<i>Martucciello G</i>	76, 77
<i>Fierbinteanu-Braticevici C</i>	74, 75	<i>Massari M</i>	79
<i>Franciotti D</i>	68	<i>Mayer EA</i>	26
<i>Garganese MC</i>	71	<i>Mearin F</i>	25
<i>Gaudio E</i>	73	<i>Menarini M</i>	78
<i>Gionchetti P</i>	42	<i>Miele E</i>	45
<i>Grant Thompson W</i>	55	<i>Minty I</i>	77
<i>Grassini M</i>	70	<i>Morselli C</i>	42
<i>Green S</i>	77	<i>Mueller-Lissner S</i>	51
<i>Guarino M</i>	73	<i>Navino M</i>	70
<i>Habib FI</i>	47, 76	<i>Negreanu L</i>	75
<i>Holtmann GJ</i>	20	<i>Niola P</i>	70
<i>Hsu A</i>	70	<i>Olteanu D</i>	72
<i>Iannoni C</i>	74	<i>Pace F</i>	40
<i>Irvine EJ</i>	36	<i>Pallotta N</i>	49, 74
<i>Kamm MA</i>	46	<i>Pallotta S</i>	40
<i>Lammers KM</i>	42	<i>Pane A</i>	71
<i>Latella G</i>	73	<i>Paoletti M</i>	74
<i>Law N-M</i>	69, 70	<i>Pasquale L</i>	75
<i>Lo C</i>	70	<i>Pillastrini P</i>	78
<i>Locke GR III</i>	22	<i>Pistoso S</i>	72
<i>Loo C-M</i>	70	<i>Piubello W</i>	72

Author Index

	<i>Page</i>		<i>Page</i>
<i>Poletti E</i>	78	<i>Tebaldi M</i>	72
<i>Porcelli P</i>	69	<i>Tonini M</i>	56
<i>Quigley EMM</i>	30	<i>Torrioni F</i>	71
<i>Rando G</i>	79	<i>Tribus L</i>	74
<i>Read N</i>	24	<i>Usvat R</i>	75
<i>Rispo A</i>	75	<i>Varma J</i>	77
<i>Rizzello F</i>	42	<i>Vatev HV</i>	68
<i>Romano P</i>	77	<i>Venerucci F</i>	76
<i>Sanders KM</i>	71	<i>Verna C</i>	70
<i>Sarnelli G</i>	75	<i>Veruschi A</i>	73
<i>Sbona C</i>	76	<i>Ward SM</i>	71
<i>Scarpignato C</i>	60	<i>Whitehead WE</i>	22
<i>Severi C</i>	73	<i>Whorwell PJ</i>	35
<i>Sferra R</i>	73	<i>Wiel Marin A</i>	79
<i>Spiller RC</i>	34	<i>Wooff D</i>	77
<i>Staiano A</i>	54	<i>Yanagida H</i>	71
<i>Tack J</i>	44	<i>Yiannakou Y</i>	77
<i>Tambasco R</i>	42	<i>Zanella A</i>	79
<i>Tan N-G</i>	70	<i>Zanninelli G</i>	73
<i>Tattoli I</i>	73		

Index

of contents

Programme General Information 3

Programme Scientific Information 7

Lectures 1 ⇨ 37 13

Abstracts 1 ⇨ 24 63

Author Index Lectures and Abstracts 81



ANEMGI ONLUS

ASSOCIAZIONE PER LA NEUROGASTROENTEROLOGIA E LA MOTILITÀ GASTROINTESTINALE

V.le M. Pilsudski, 118 - 00197 Roma - Italy - Tel. e Fax +39 068078303

e-mail: anemgi@anemgi.org

www.anemgi.org

Public Relation and Publishing Office: Emanuela Crescini

MESSAGGI