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CATEGORISATION OF DISORDERS OF INTESTINAL FUNCTION

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INTRODUCTION

In Medicine there is a long tradition to categorise disease states. In general these categories are addressed as diagnoses. Categorisation of diseases is usually based upon structural or biochemical abnormalities. Diagnosing specific disorders - which basically represents categorisation of diseases - intends to group conditions with common underlying abnormalities. Thus categorisation facilitates treatment by grouping disorders with common pathophysiologies. In addition, categorisation of diseases may allow predicting the prognosis of a given patient with regard to response to therapy or the long term outcome. Similarly, categorisation of so called functional gastrointestinal disorders (disorders of functional 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 testing ¹. Thus the classic approach of categorisation based upon structural or biochemical abnormalities is not feasible in patients with functional gastrointestinal disorders.

CATEGORISATION BASED UPON SYMPTOMS

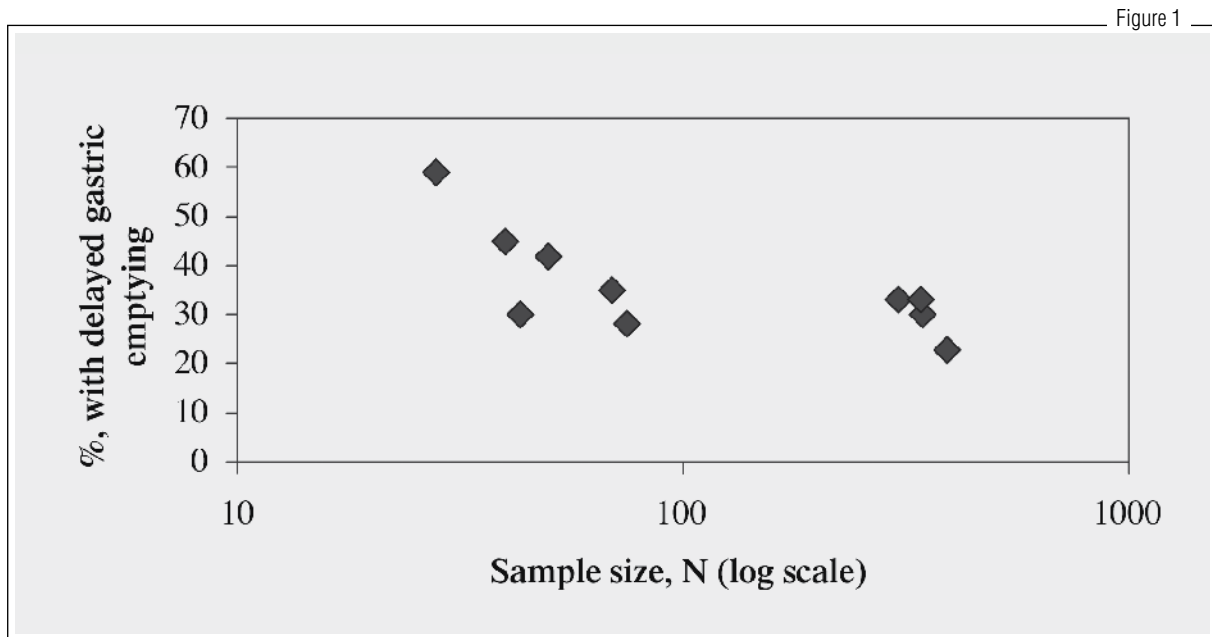
In the absence of structural lesions attempts have been made to categorise functional disorders based upon the symptoms. Characteristics of symptoms (e.g. fullness, pain, nausea, bloating) as well as the localisation of symptoms (upper or lower gut), were used to categorize patients into more or less 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 methodologies ²⁻⁴.

Unfortunately symptom categories overlap ⁵. 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 stability over time. Indeed, a large proportion of patients fluctuate between functional dyspepsia, IBS or a combination of both ⁶.

CATEGORISATION 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 disorders ⁷. It appears logic to categorize patients based upon underlying abnormalities. A remarkable amount of data is now available with regard to gastric emptying. While the early (small) studies demonstrated a remarkable proportion of patients with delayed gastric emptying, larger studies were not able to confirm this. Interestingly, the proportion of patients with delayed gastric emptying is inversely related to the sample size (Figure 1). This may suggest that in the early studies with usually small samples of patients, subjects with more severely impaired function were recruited.

Only limited number of studies has 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-health care seeking) subjects with dyspepsia ⁸. 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 sub-



Proportion of patients with delayed gastric emptying and sample size. There is an inverse relation between proportion of patients with delayed gastric emptying and the sample size. This may suggest a referral bias towards more severely impaired function in the initial studies

groups of patients⁹.

In addition while some symptoms (i.e. early satiety or fullness) were more severe or prevalent in patients with delayed gastric emptying, the association between disordered function and symptoms is inconsistent hence a remarkable proportion of patients with normal gastric emptying also had these symptoms¹⁰. In addition, there is lack of data that demonstrates that normalisation of disordered gastric emptying is associated with improvement of symptoms.

While a considerable amount of data is now available for gastric emptying, there is as yet only limited data available on visceral sensory function¹¹⁻¹⁴ and fundic relaxation in response to a meal¹⁵⁻²¹. So far the evidence of a close relation between symptoms and impaired fundic relaxation is lacking.

CATEGORISATION BASED UPON INITIATING EVENTS

It is now believed, that a proportion of patients manifest symptoms after an acute gastrointestinal infection²². 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 $\beta 3$ (GNB3) subunit gene polymorphisms (C825T) and polymorphisms of 5-HT transporter genes and other molecular markers are suitable for categorisation of functional GI disorders. Thus, relevant polymorphisms of genes with immunomodulating and/or neuromodulating features (OPRM1, IL-4, IL-4R, TNF α) may also play a role for 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. In the presence of specific hereditary factors (e.g., specific polymorphisms of adrenergic receptors or proinflammatory cytokine expression, specific GNB3 genotypes), environmental factors that are usually not suitable to cause long lasting alterations of function are linked to the manifestation of symptoms. While research in the field of the molecular markers or risk factors may contribute to our understanding of the underlying pathophysiology, it is as yet not proven that these molecular markers are of value for the categorisation of patients with functional GI disorders.

Table 1

SUGGESTED MULTIDIMENSIONAL CATEGORISATION OF FGID	
Global category	Functional gastrointestinal disorder
Predominant type	e.g. functional dyspepsia
Disordered function	e.g. delayed gastric emptying, impaired fundic relaxation
Comorbidity	e.g. anxiety disorder, depression
Trigger	e.g. postinfectious
Genetic factor	GNB3, 5HTT Polymorphism

SUMMARY AND CONCLUSIONS

Categorisation of functional gastrointestinal disorders serves various purposes. The probably most important is to guide therapy. Thus a specific category should predict the likelihood of response to a particular therapy. Unfortunately there is limited evidence that the current categorisations actually serve this purpose.

Current definitions are as yet consensus based. These categorisations (definitions) allow standardizing the approach to patients with these disorders in the clinical setting and in clinical trials. While the current symptom based definitions are important milestones, there are a number of limitations that need to be recognized. The current categorisations are mainly consensus-based and empiric validation in various populations is lacking. Furthermore, there are no data that sufficiently support the assumption that the categorisation is of value to target therapy or predict the long term outcome.

While the symptom based categorisation is the most important and the most frequently utilised approach, categorisation based upon abnormalities of function is an alternate approach. Gastric emptying, fundic relaxation and sensory thresholds are the most frequently used parameters. Unfortunately the clinical value with regard to the response to therapy or the long term outcome is lacking.

Thus there is as yet no perfect categorisation that serves the various purposes. In the routine clinical setting the assessment of the most dominant symptom might be sufficient and appropriate. In the context of clinical trials symptoms a more complex categorisation 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 categorisation should include a dimension of the symptoms 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 gene (Table 1).

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**APPROACH TO THE PATIENT WITH
FUNCTIONAL GASTROINTESTINAL DISORDERS**

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I PROBLEMI GASTROENTEROLOGICI NEL PAZIENTE CON MALATTIA DI PARKINSON

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I disturbi gastrointestinali sono stati segnalati già nel 1817 da Sir James Parkinson nella descrizione originaria della malattia che da lui prende il nome “Essay of the shaking palsy”, e più recentemente è stato persino ipotizzato che in alcuni pazienti la stipsi possa rappresentare un sintomo precoce della malattia ¹.

La gravità dei disturbi sembra direttamente correlata allo stadio e alla durata della Malattia di Parkinson (MP), suggerendo che essi siano parte integrante della sua storia naturale ². Frequentemente i disturbi gastrointestinali (GI) pesano negativamente sulla qualità di vita dei pazienti, possono essere causa di complicanze e interferire con il trattamento farmacologico.

I disturbi correlati alla funzione dei muscoli scheletrici (deglutizione, evacuazione) trovano una spiegazione fisiopatologica nelle alterazioni responsabili della MP ³ e presentano alcune caratteristiche proprie della sindrome neurologica quali la fluttuazione durante i periodi di on ed off ⁴, la correlazione con la gravità dello stadio di malattia e, almeno in situazioni di studio, una risposta positiva alla terapia specifica con apomorfina e/o farmaci dopaminergici ⁵.

La deplezione di dopamina nei neuroni enterici e la presenza dei corpi di Lewy, reperti caratteri-

stici della MP, sono state riscontrate nel plesso mioenterico a vari livelli del tratto gastrointestinale ^{5,6,7}, suggerendo un coinvolgimento primitivo anche dell'apparato neuro-muscolare gastrointestinale.

Per stabilire la prevalenza dei disturbi GI nella MP un questionario autocompilato sui disturbi GI, standardizzato e validato, è stato redatto dall'Anemgi onlus e diffuso ai pazienti mediante Associazioni MP e personale degli ambulatori di Neurologia. Almeno un disturbo GI era riferito nel 90% di 138 questionari. I sintomi GI più frequenti erano: disfagia (39%), pirosi (20%), dolore toracico (9,4%), rigurgito esofageo acido (9,4%). La disfagia era associata a pirosi in 23 casi e a dolore toracico in 7. Il dolore addominale era presente nel 33,3% dei casi, la stipsi nel 49%, il 51% riferiva uso costante di lassativi e il 29% incontinenza anale ⁸. Inoltre i pazienti hanno spesso incompetenza labiale con fuoriuscita di saliva, nausea e disturbi dispeptici.

I meccanismi delle alterazioni viscerali restano incerti, la terapia anti-Parkinson sembra avere su di essi minore efficacia e non sempre c'è corrispondenza tra tipo di sintomo e alterazione fisiopatologica ². Questa variabilità impone, almeno nei pazienti maggiormente impegnati, uno

studio diagnostico appropriato per identificare i meccanismi fisiopatologici compromessi nel singolo paziente.

DISFAGIA

I disturbi della deglutizione costituiscono un problema clinico rilevante, che induce i malati a ridurre l'alimentazione con conseguente denutrizione, ostacola l'assunzione della terapia orale, e soprattutto può essere causa di complicanze broncopulmonari gravi. L'alterazione delle strutture muscolari oro-faringee e linguali può tradursi inoltre in disturbi della fonazione e la ridotta frequenza dell'atto deglutitorio, comportando accumulo di saliva nel cavo orale, determina la fuoriuscita di saliva dalle labbra ^{9,10}.

La disfagia nella MP sembra dovuta ad alterazioni sia della muscolatura striata (controllo dopaminergico) sia della muscolatura liscia (controllo autonomo) ¹¹, e può interessare tutte le fasi della deglutizione.

Nessuna caratteristica clinica è predittiva della presenza e/o del tipo di alterazione funzionale; la disfagia è più spesso presente nelle forme avanzate di malattia, ma è stata descritta anche come sintomo di presentazione della MP. D'altra parte è stato anche descritto che la disfagia, in un

gruppo di soggetti, recede con terapia antisecretoria acida, suggerendo che possa essere sintomo di malattia da reflusso gastro-esofageo¹².

Nei casi maggiormente compromessi, per identificare i meccanismi motori alterati e guidare la terapia è indicato eseguire un esame videofluoroscopico nella deglutizione ed una pH-manometria esofagea.

STIPSI

La stipsi cronica è il sintomo gastrointestinale più frequentemente riferito dai pazienti con MP e può costituire una delle manifestazioni d'esordio della malattia¹³. Sebbene interpretata come parte della MP sin dalle prime descrizioni, i pazienti non sempre associano le alterazioni dell'alvo all'aspetto neurologico, con il risultato che la stitichezza viene trascurata o mal gestita. L'uso continuativo e incongruo di lassativi, spesso assunti in dosi crescenti per mantenerne l'efficacia, può causare la comparsa di dolori addominali e diarrea con il rischio di incontinenza fecale e altri effetti collaterali.^{13,14}

La stipsi inoltre influenza negativamente la qualità di vita dei pazienti, perchè oltre ad essere un sintomo fastidioso, può contribuire all'insorgenza di altri disturbi gastrointestinali e può influenzare, direttamente o indirettamente con l'uso di lassativi, l'assorbimento dei farmaci assunti per via orale. Quest'ultima eventualità può avere come conseguenza la perdita del controllo sui sintomi neurologici e quindi un aggravamento del quadro di malattia.

Il meccanismo responsabile della stipsi nella MP non è tuttora completamente noto, ma è verosimilmente sostenuto da una patogenesi multifattoriale. In alcuni casi la stipsi può precedere l'insorgenza della malattia neurologica e aggravarsi con il progredire di questa. Il coinvolgimento del sistema nervoso autonomo e del sistema nervoso centrale concorre nel provocare alterazioni della funzione motoria del colon e/o della muscolatura pelvica, la cui espressione clinica comune è la stitichezza. Alla patogenesi della stitichezza possono contribuire: l'alterato controllo dell'attività motoria del colon e della muscolatura anale e la terapia farmacologica anti-parkinson. Una normale contrattilità del colon con contrazioni segmentanti e propagate garantisce il mescolamento e la progressione del contenuto intestinale. La fase di espulsione delle feci è invece il risultato della coordinazione tra la contrazione del diaframma e della muscolatura addominale (torchio addominale) e il rilasciamento della muscolatura del pavimento pelvico (muscolo pubo-rettale, sfintere anale esterno).

Poichè nella MP può esistere una compromissione di entrambi i distretti muscolari, si possono verificare sia un'alterata attività propulsiva del colon con un rallentato transito intestinale, sia una rigidità della muscolatura anale con conseguente incoordinazione che si traduce in difficoltà all'espulsione delle feci. Entrambe queste alterazioni possono causare stitichezza che può presentarsi come ridotta frequenza delle evacuazioni (~29% dei pazienti con MP) e dischezia (~66% dei pazienti con MP), ma

frequentemente i due sintomi sono associati.

Tra meccanismo fisiopatologico e presentazione clinica non c'è però corrispondenza univoca: il 30% circa dei parkinsoniani con frequenza dell'alvo inferiore a 3 evacuazioni per settimana presenta anche dissinergia pelvica e circa il 60% di coloro che lamentano difficoltà nell'evacuazione presenta un rallentato transito nel colon. Nel singolo paziente quindi non sempre è possibile risalire dal sintomo di presentazione al meccanismo patogenetico. Per questo motivo, nei casi più impegnativi, per meglio indirizzare la terapia è utile il ricorso ad esami diagnostici funzionali: studio del transito intestinale - totale e segmentario - mediante indicatori radio-opachi, manometria rettoanale, elettromiografia del pavimento pelvico, defecografia.

SVUOTAMENTO GASTRICO E ASSORBIMENTO DELLA LEVODOPA

Lo svuotamento gastrico ritardato è un evento frequente nei pazienti affetti da MP e può causare diversi disturbi quali senso di sazietà precoce, distensione addominale, nausea, vomito, che talora inducono a ridurre l'introito alimentare con conseguente perdita di peso e malnutrizione. La Levodopa (L-DOPA) assunta per via orale è il trattamento più efficace della MP. Essa non è assorbita a livello dello stomaco, ma del duodeno e del digiuno. La velocità e la quantità di L-DOPA assorbita a livello intestinale sono strettamente dipendenti dal tempo di svuotamento gastrico che è diverso per la

componente solida e quella liquida. La componente liquida non necessita infatti della funzione motoria antrale ed è più rapidamente avviata verso il duodeno.

In presenza di rallentato svuotamento gastrico, la prolungata permanenza della L-DOPA nello stomaco ha tre conseguenze negative. La prima è che viene ritardato l'arrivo del farmaco nei tratti intestinali deputati all'assorbimento. La seconda è che, per azione della Dopa-decarbossilasi presente nella mucosa gastrica, il farmaco viene convertito in dopamina nello stomaco diminuendo la sua disponibilità a livello del sistema nervoso centrale. La terza è che la dopamina formatasi nello stomaco tenderà a stimolare i recettori situati a livello dello stomaco con conseguente ipotonia delle pareti gastriche e ulteriore rallentamento dello svuotamento gastrico.

Un assorbimento insufficiente o ritardato di L-DOPA può essere la causa di una fase di "on" ritardato ed insufficiente in pazienti con Parkinson avanzato e stomaco atonico.

È stato visto infatti che, talora, nei pazienti con MP la compressa di L-DOPA può rimanere nello stomaco per molto tempo non raggiungendo quindi il sito intestinale di assorbimento e ritardando l'inizio dell'effetto terapeutico.

Una fase ritardata o insufficiente di "on" avviene più frequentemente dopo assunzione di L-DOPA prima del pasto, che a sua volta può alterare la solubilità del farmaco e rallentare ulteriormente lo svuotamento gastrico. I livelli plasmatici e la risposta clinica sono risultati più precoci dopo assunzione di melevodopa che levodopa in preparazione solida¹⁵, per l'elevata solubilità della melevodopa che, diversamente dalla preparazione solida, consente al farmaco di giungere immediatamente a contatto con la mucosa duodenale.

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THE PLACEBO EFFECT AND FUNCTIONAL GASTROINTESTINAL DISORDERS

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“... until recently, the history of medical treatment is essentially the history of the placebo effect”

A. K. Shapiro and E. Shapiro, 1999 ¹

Any discussion of treatments for the functional gastrointestinal disorders [FGID] should emphasize the most effective treatment of all – the placebo effect. Indeed, were it not for this phenomenon, doctors would not likely exist, and healers in all societies would be far less successful ². From the beginning, successful healers instinctively employed the placebo effect and understood that most ailments ameliorate eventually. Mastery of these two phenomena is the “art of Medicine”. Paradoxically, modern doctors, endowed at last with effective treatments and many cures, often fail to deploy the skills and attributes that originally secured their stature in society. In this chapter, I will discuss three themes: that the *placebo effect* not the placebo is an important component of all healing; that it has important implications for the treatment of the FGID; and that physicians and others must strive to optimize it.

THE PLACEBO EFFECT, NOT THE PLACEBO

Do placebos have power?

Hrobjartsson and Gotzsche ³ performed a systematic review of 114 randomized clinical trials (RCT)

that included both a group that received placebo and another group that received no treatment. Many of these trials were testing a treatment, but the authors examined only data from the placebo and “no treatment” groups. Except for a few small pain trials, they found little difference in the outcomes between the two groups, and concluded that the placebo had no power. The authors miss the point. Each trial included both control groups and managed them under similar conditions of monitoring and continuing care that are known to optimize the doctor/patient relationship -- and hence the placebo effect.

To illustrate, consider one of the trials reviewed by Hrobjartsson and Gotzsche. Patients with an indefinite diagnosis comprise about half those seen in primary care ⁴. Thomas ⁵ randomized 200 such patients from his general practice into two groups of 100; the first subjected to a positive approach and the second to a neutral one (Table 1). Those in the first group were given a firm diagnosis and told that they would be better in a few days. The patients in the second group were told, “I cannot be certain what is the matter with you.” Half of the patients in each group received a placebo pill (thiamine), with words indicating it would help them

Table 1

POSITIVE PHYSICIAN ATTITUDE VERSUS PILLS IN ACHIEVING A PLACEBO EFFECT ⁵

Two hundred consecutive general practice patients with undiagnosed complaints:

	n*	Diagnosis	Physician Attitude	Improved **
Positive	50	yes	“You will be better soon...”	32/50 (64%)
Positive + Pills	50	yes	“Pills will help...”	32/50 (64%)
Negative	50	no	“I don’t know what you have...”	18/50 (36%)
Negative + Pills	50	no	“I don’t know if pills will help...”	21/50 (42%)

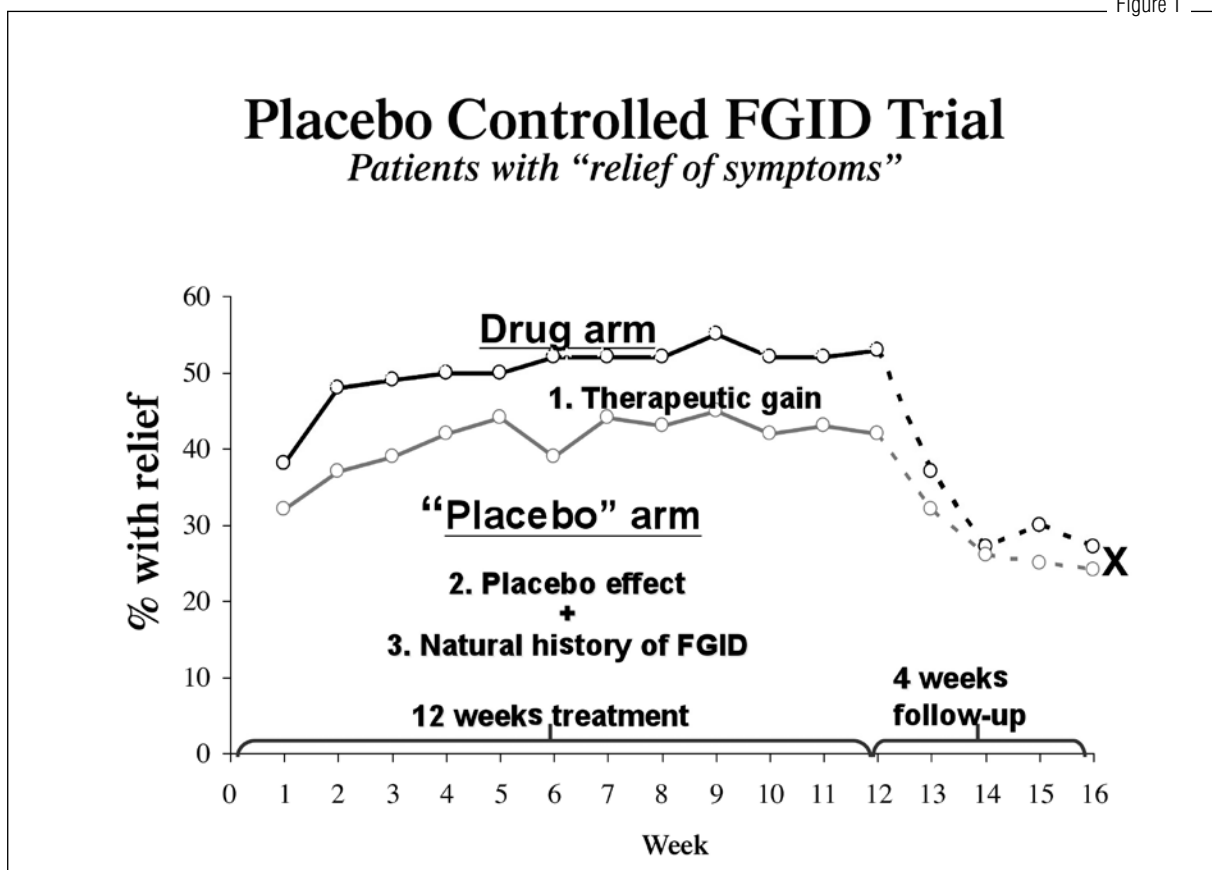
*n = number of subjects

***‘Positive’ vs ‘negative’ treatment p<.005

in the first group, and without such encouragement in the second. Sixty-four percent of the patients treated with a diagnosis and encouragement improved, compared to only 39 percent of the undiagnosed, unencouraged group. The giving of a placebo pill made no difference in either group. Clearly, the doctor himself can be a powerful therapeutic agent – 25% of patients improved with

nothing more than encouragement and a diagnosis. A placebo treatment, be it a pill, a diet, a surgical procedure, an acupuncture treatment – even psychotherapy – has no power in itself, but the circumstances, and how treatment is given by a healer to an ill person may be very powerful medicine indeed.

Figure 1



A hypothetical randomized, placebo-controlled trial of a drug treatment of a FGID illustrating the components of a therapeutic response. The difference between the number of “improved” patients on *drug* (black line) and on placebo (grey line) is the *therapeutic gain*. The 10-12 percent gain is typical of that of many drugs achieving regulatory approval for the treatment of FGID.

About 40 percent of the patients improved with placebo. When drug and placebo were stopped at the end of the study, the number of improved patients fell (X), but not to zero. This decrease may represent the loss of the placebo effect in both groups of patients, less the therapeutic gain in the drug-treated patients. FGIDs naturally fluctuate in severity. Therefore, the approximately 25 percent improvement after withdrawal (X) may indicate what the outcome would have been had no treatment been given. These two influences, placebo effect and natural change are at work in all therapeutic encounters.

Obviously, these powerful improvement tendencies are present in subjects given the test drug as well as those given a placebo. Indeed, were a drug’s benefit limited to the therapeutic gain of 10-12%, its clinical value would be unimpressive. In FGID, natural improvement and the placebo effect may be the most powerful, indeed the only, components of a treatment’s success.

The placebo effect in clinical trials

Figure 1 illustrates a hypothetical RCT of a drug for the treatment of a FGID ^{2,6}. All the entered subjects weekly recorded whether they had achieved “relief of symptoms.” The investigators randomly assigned them to one of two groups -- members of the first group received the drug to be tested and those in the control group received an outwardly identical, but inert placebo. Neither doctors nor patients knew which treatment they received (a double blind study). Notice that each week during treatment more patients reported pain relief on the drug than on the placebo. The difference between the two is the *therapeutic gain*, the holy grail of clinical trials. This difference, if statistically significant, indicates that the drug is effective.

In both groups, most of the observed improvement is *not* due to the drug. This effect, imprecisely called the *placebo response*, has two main components, the *placebo effect* and the *natural history of the disease* ⁷. Since FGID tends to fluctuate, some patients would have improved with no treatment at all. In the figure, notice that when the drug is stopped the benefit falls to a point (X) but not to the baseline. The benefit declines to a similar level (X) when the placebo is discontinued. The fall to (X) roughly represents the loss of the placebo effect (and the therapeutic gain in the treated group), and (X) represents the subjects’ likely status if no treatment had been given (i.e. the improvement attributable to the “natural” course of the disease). Such data are the most compelling scientific evidence of a placebo effect. Sometimes the meaningless term “non-specific effects” describes other components of the placebo response. “Non-specific” circumstances of treatment and the doctor-patient relationship are both determinants of the placebo effect.

Consider the Therapeutic Equation:

Treatment benefit = Therapeutic gain + Natural history of illness + Placebo effect

Where,

Therapeutic gain is the effect on a patient’s symptom or pathological abnormality by a drug, a diet, a procedure or a psychological treatment.

Natural history is the state of a patient’s symptom or pathological abnormality that would exist at the

end of the trial if no treatment were given.

Placebo effect is an improvement in a patient’s illness that is due neither to the properties of a treatment, nor to the natural history of the symptom or disease. This includes so-called “non-specific effects,” and is termed the “*true placebo effect*” ⁷.

“Natural” History

The FGID are chronic, often-painful conditions of fluctuating intensity. Patients report symptoms or enter trials when their symptoms are bothersome, so there is a tendency for them to improve over the course of any treatment (regression to the mean). Of course, improvement during a clinical trial is not at all natural. Even when given a placebo, the patient’s experiences with the treatment may favour improvement. Parallel interventions such as improved diet and patient education may also be beneficial. Healers recognize the tendency for many conditions to improve. Voltaire once said that a good physician was one who successfully amused his patients until they became well. Of course, patients with a fatal disease such as cancer may benefit less. While this essay is about the placebo effect, it is important to keep natural history in mind when considering the therapeutic effect of any treatment.

MYTHS ABOUT THE PLACEBO EFFECT

The Placebo Effect is Temporary

There are misconceptions about the placebo effect. Some consider it a temporary phenomenon – three months is commonly quoted. Reports in the surgical literature indicate that the relief of pain after an appendectomy or cholecystectomy lasts about three months when the removed organ is found to be normal. That is, the pain was due to something else, probably a FGID. However, several studies of other diseases such as rheumatoid arthritis, angina pectoris and ulcerative colitis indicate a more lasting placebo effect is possible ^{8,9}. One long-term FGID trial demonstrated a sustained benefit over a year ¹⁰. The effect is enhanced by frequent reassuring doctor visits ¹¹.

Placebos can cure disease

Some have claimed that the placebo effect is all-powerful, and can evoke “miracle” cures. Here we

confront the indistinct line between disease and illness. There is no evidence that the placebo effect can shrink cancers, clean out arteriosclerotic arteries or reduce inflammation, but it can make ill people feel better. The FGID, which lack such pathology, are especially suited to exploitation of the placebo effect.

The “Placebo Responder”

Another myth is that certain individuals are “placebo responders”. This is not so. No personal characteristics permit one to predict a person’s response to a placebo treatment. In fact, we may all be placebo responders at certain vulnerable times in our lives. This myth is especially misleading if it tempts investigators to try to minimize the response by excluding those patients from a trial who respond to a placebo during a baseline period. Not only is this unsuccessful, but also such a procedure impairs a trial’s generalizability (see below). Moreover, as we shall see, an active treatment following a placebo is less effective than otherwise, thereby further compromising the trial.

The Placebo Effect is Unethical

Deliberate deception such as the prescribing of a ‘useless’ sugar pill to an unsuspecting person is unethical. However, maximizing the effect of a legitimate treatment through compassion and reassuring explanation risks no deception, and is certainly ethical.

A High Placebo Effect impairs the Validation of Effective Treatments

Some pharmaceutical representatives and others misunderstand the science of clinical trials, and may claim that RCTs would show their product’s benefit to greater advantage were it not for the placebo effect. This is nonsense. If properly executed, the treatment and placebo arms of a RCT should differ only in the presence or absence of the test treatment. Natural history and placebo effects should be identical. The placebo effect is not the enemy, and wise pharmaceutical marketers should encourage their drug’s enthusiastic and compassionate administration under optimal conditions.

Placebos are Dummy Pills

While the term placebo originally denoted fake treatments, modern doctors are more likely to think of dummy pills in clinical trials. This implies an-

other myth – that only pills may serve as placebos. In the 1950s, surgeons claimed that ligation of the internal mammary arteries improved coronary blood flow and relieved angina pectoris. They claimed that 90 percent of their patients improved after this popular procedure, but later doubts set in. In 1959 two small RCTs compared the relief of angina after incision and ligation of the internal mammary arteries with relief by ligation alone^{12,13}. Improvement was 35 percent in each group, and this useless procedure was swiftly abandoned. The conditions surrounding surgery are ideal for the placebo effect. The care and attention by nurses and anaesthetists; trust in the surgeon; hopeful expectations; and investment of time, money and pain in the project all occur amid great ceremony and drama. Surgical trials encounter unique ethical dilemmas, and surgical RCTs are rare. Nevertheless, the placebo effect is powerful in surgery, and it should stimulate critical thinking about some contemporary operations. The point here is that a placebo effect is possible and important in all healing encounters, not just through a dummy pill.

THE PLACEBO EFFECT AND PATIENT CARE

Placebo effects have two important implications for the practice of Medicine – indeed for all who care for the sick. The first is that the effect’s potential in all therapeutic activity means that we must prove that treatments are useful in themselves. The second is that the manner of a treatment’s delivery may enhance, or reduce, its effectiveness.

Evidence-based Medicine

The history of medicine is replete with examples of useless or harmful treatments whose employment is explicable only by the tendency of many symptoms to improve and the placebo effect. Before effective diuretics were available, blood letting reduced the load on a failing heart. Hence, venesection may have been useful as a treatment for oedema, but it existed for centuries as treatment for all sorts of other maladies for which it could offer no benefit. George Washington’s death from quinsy was undoubtedly hastened by his physicians’ ill-advised blood-letting¹⁴.

A century ago, some claimed that absorption of toxins from the colon led to chronic conditions

such as depression, senility, rheumatoid arthritis and hair loss¹⁵. Enthusiasts blamed such illnesses on colon stasis where resident bacteria caused *autointoxication*, necessitating ritual purging or even colectomy. Today, such notions persist in the misuse of colonic irrigations and laxatives. We have seen that internal mammary artery ligation exerts a strong placebo effect on angina patients that obscured the uselessness of the procedure itself. How many currently respectable medical treatments fit this category? Do complementary and alternative medicines owe their existence to the ubiquitous placebo effect?

Evidence-based medicine is a late twentieth century phenomenon. So far, it applies to relatively few contemporary treatments, other than new prescription drugs. The anecdote, the testimonial, the series, and the enthusiastic therapeutic headline serve us badly. The lessons of the placebo effect and the healing properties of time should signal a healthy scepticism, and renewed effort to prove what doctors do is truly beneficial.

The Doctor/Patient Relationship

There is another, equally important implication of the placebo effect. A successful interaction between the healer and an ill person can enhance the benefit of any treatment. Anthropologists remind us that every recorded society has a person or persons endowed with healing power. Whether called a shaman, a medicine man or simply a chief or tribal leader, he or she is sought by the ill and the troubled for cure and solace. In western societies, the doctor fulfils that role¹⁶.

Despite possessing few or no instruments of effective healing, our medical predecessors were revered for their knowledge, compassion and wisdom. With little to offer but time, they attended the sick and shared life and death battles with patients and their families. As the quote at the beginning of this chapter implies, much of the doctor's success depended upon the placebo effect. It is ironic that notwithstanding modern medicine's technological successes, doctors' stature in society has declined, and many patients find their healing encounters unsatisfactory. Over reliant on technologic successes, and increasingly subject to outside pressures and lack of time, doctors' contacts with patients have become brief and impersonal. The elements that promote the placebo effect are missing as the urgency of the clinic dictate a quick prescrip-

tion or procedure.

Such was the power of the medicine men in many primitive societies that they could do harm as well as good^{17;18}. Voodoo and "the evil eye" describe harmful (nocebo) effects resulting from a malevolent relationship between an authority figure and an ill or troubled person. Contrary to the placebo effect, the *nocebo effect* results from an unsatisfactory "therapeutic" encounter. In a randomized, controlled trial, it is no accident that subjects assigned to the placebo group suffer side effects similar to those of the treated patients. Informed consent and concealed allocation demand that all trial subjects be aware of possible risks. The power of suggestion does the rest. In modern medicine, an unsatisfactory doctor/patient encounter may amplify an unsatisfactory outcome and end in malpractice litigation, when lack of communication, not malpractice is the problem. Consider again the therapeutic equation:

$$\textit{Treatment benefit} = \textit{Therapeutic gain} + \textit{Natural history of illness} - \textit{Nocebo effect}$$

A strong nocebo effect can cancel the benefit of an effective treatment.

OPTIMIZING THE PLACEBO EFFECT

The placebo effect is important to all therapy, and deserves serious study. Rather than the enemy -- a foil for "evidence based medicine," it should be an important clinical tool. Several factors may promote placebo effects:

Allaying Anxiety and Fear

Every pain includes sensory, emotional and cognitive awareness. Some pains are sensed predominantly through the peripheral nervous system, and are assuaged by analgesics. Others are felt mainly through the central nervous system (CNS)^{19;20}. Each mechanism demands attention. A boy bruises his knee. Through nerve transmission from knee to brain, he instantly senses pain. However, no specific treatment of the knee arrests his cry, only his mother's comforting and reassuring embrace. In contrast, the CNS plays a significant role in the perception of chronic pain and other symptoms, Anxiety and fear are often present. These affective-motivational and cognitive dimensions of a symp-

tom are typical of chronic and unexplained disorders. Despite patients' bitter complaints, FGIDs often lack objective features such as withdrawal and tenderness when touched on the affected area. The psychological and social reactions of FGID patients often prevent accurate description, and obscure the exact location and nature of the painful stimulus. A precise physical cause is not identified. Unlike in acute pain, analgesics are relatively ineffective, but psychoactive drugs such as antidepressants (sometimes in small doses) may help.

Chronic symptoms that are unresponsive to drugs cause many patients with FGIDs to become disillusioned with conventional medicine. Alternative therapies delivered in a manner that allays anxiety or salves emotional hurts can achieve positive results -- at least for a time. The enthusiastic administration of a "promising" treatment could lessen the anxiety component of a symptom. A doctor's ability to counter the anxiety and fear of someone with a FGID may greatly improve the outcome.

Conditioned Response

Many people associate relief of their symptoms with past treatments so that repetition engenders a conditioned response. Subtle favourable experiences with doctors, medicines, or other healing encounters have similar effects. Subjects, who as children were excused from school or received treats and comforting along with their treatments, may become conditioned to expect such perks and may even use illness to achieve special benefits later in life ²¹.

Placebo analgesia can be "conditioned." Researchers told two groups of 10 subjects that they were to receive an analgesic that was in fact a placebo ²². They surreptitiously paired placebo administration with an increased painful stimulus for the first group and a decreased stimulus for the second group. The subjects who originally had decreased pain while on placebo, experienced greater relief from a second experimental pain with placebo. Reduced pain paired with a placebo (conditioned stimulus), predicts relief of another pain with the placebo (conditioned response).

In some trials, subjects are "crossed-over" from a treatment period to a placebo period or vice versa so that each subject is exposed sequentially to the treatment and the placebo control. Other trials sometimes include a two-week placebo run-in period in a vain attempt to eliminate placebo respond-

ers. However, in a crossover trial, the placebo effect was greater if it was given after the active drug ²⁰. Conversely, the effect of a drug was less when given after a placebo. Patients switched from an active analgesic to placebo have pain relief longer than if treatment was abruptly stopped ²³. After treatment with the drug atenolol, blood pressure remained lower on placebo than if no pills were substituted ^{24,25}. Therefore, crossover trials or placebo run-in periods may be counterproductive, and obscure a treatment's benefit.

Expectation

FGID patients are more likely to improve if they expect and desire a treatment to help them ¹⁹. Improvement is reinforced if the doctor adds encouragement, and if the patient's attitude is positive ⁵. If a person expects caffeine or alcohol to improve his performance or well-being, it is more likely to do so ^{9,26}. An inert substance creates a greater expectancy of benefit if it is injected than if it is given in a pill. Even the colour and size of pills can influence a patient's expectations ¹⁶.

Conditioning and expectancy may be interrelated. In a clinical trial, ²⁷ investigators compared branded and unbranded analgesics in women who were previously either users or non-users of the brand. The active drug proved to be more effective when branded, but even the placebo was more effective when taken from a branded rather than from a plain package. Both the branded drug and the branded placebo were more effective among those who regularly used the brand prior to the trial. Previous users of the drug were conditioned either to get pain relief when taking a branded placebo, or the sight of the brand name on the package caused them to expect relief.

The prospect of surgery engenders great expectations. The pre-operative rituals and commitments accompanying an operation can reinforce powerfully the expectation of a positive result. Moreover, when patients are involved in the decision to operate and even the choice of operation, there is a strong incentive for them to feel better ²⁸. Otherwise, they must admit to themselves, relatives, and others that they made a mistake. Postoperative improvement may be even greater if a patient has paid for the surgery. Great expectations must also accentuate the disillusionment if the operation turns out badly -- a nocebo effect.

Expectation of pain relief can be very specific. In

volunteers, subcutaneous injection of the irritant capsaicin induced a painful local reaction in all four limbs²⁹. Application of an inert cream relieved the pain only in the limbs where it was applied. In addition, the narcotic antagonist, naloxone, cancelled the pain-relieving effect of the cream. Expecting that the placebo cream would relieve the pain made it happen. The authors speculate that a local opioid mechanism accounts for this placebo effect -- the body's natural narcotics (endorphins) are blocked by naloxone. In any case, the subjects expected and therefore experienced pain-relief only in the treated limbs.

For expectation to occur, the patient must know when treatment is given. Forty-two post thoracotomy patients were given narcotic injections for analgesia³⁰. Half the patients had the injections in plain view and were told when they were receiving them. The other 21 patients had their injections concealed and were unaware of the timing. The patients who saw the injections recorded greater pain relief. One must witness the treatment to anticipate relief.

By talking to patients and addressing their concerns, doctors encourage expectancy. Researchers¹⁶ retrospectively reviewed the case notes of 112 patients diagnosed 32 years earlier to have the irritable bowel syndrome (IBS). They recorded features of the doctor's record that gauged the strength of the doctor/patient relationship. The more of these features the researchers found in the original record, the less likely were patients to return to the doctor for IBS symptoms. Prompt attention to a patient's concerns and fears may increase their expectation of a favourable outcome, and have lasting benefits.

Culture (Placebo and Nocebo)

Throughout history, every tribe, culture, or society included medicine men and women who enjoyed great authority among their people. These individuals wielded power for good and evil. (See nocebo effect above.) They were deeply rooted in cultural traditions and people believed they could heal. Medicine men are prevalent in all cultures and must satisfy a primitive need to make sense of the menacing material world. Modern physicians assume this role in our society and should recognize the importance of their patients' culture, tradition, and ritual when establishing a healing relationship.

The Doctor

Brody^{31;32} provided the following definition of a placebo effect, "...a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacological or physiological property." Pills are unnecessary to the achievement of a placebo effect. Whatever the treatment, healers can make ill people feel better. The doctor *is* the placebo!

Usually, doctors achieve greater placebo effects than other health professionals do. Sending a pill through the mail avoids human contact and so diminishes the benefit. A doctor's healing power depends upon her reputation; her figure, manner and personality; the authority and confidence with which she delivers the treatment; and even upon such healing symbols as the office, instruments, white coat and the accompanying disinfectant aromas.

A positive approach to the FGID may be therapeutic no matter what the treatment^{5;33}. A doctor can convey compassion and encouragement through feeling the pulse, listening to a patient's concerns, and physical examination. Surgeons and gastroenterologists notice their patients' relief when they examine the abdomen or other painful part. Our predecessors braved inclement weather to attend the sick, comfort the parents of a sick child, or wait patiently at the bedside for a fever to dissipate -- and they were renowned for it. What contemporary doctor has time for such compassion! Sadly, the efficiency of modern, technologically triumphant medicine threatens the "art", which is so essential to successful FGID management.

Diagnosis and Meaning

Diagnosis can provide an understandable and satisfying explanation for an illness³². By making a diagnosis and explaining the nature of the complaint, a doctor gives her patient something tangible to explain to his friends and family. A skilfully orchestrated diagnostic test can have therapeutic as well as diagnostic benefits. Sox et al randomized 176 patients with non-cardiac chest pain into two groups. These were treated equally, except that one group was tested with an electrocardiogram and a blood creatinine phosphokinase³⁴. Despite the diagnostic imprecision of these tests, the tested group had less pain, less disability, and were more satisfied with their care than the untested group.

Diagnosis demonstrates a healer's care and concern

Table 2

FEAR OF CANCER BEFORE AND AFTER A PRIMARY CARE CONSULTATION		
	Patients with Irritable Bowel syndrome 76 patients	Patients with 'Organic' Disease 100 patients
Worried their symptoms meant cancer	45%	27% p<.02
Reassured by doctor that they did not have cancer	29%	all

From W Grant Thompson et al ³⁵

for a patient's suffering, confers meaning to his symptoms, and "now that we know what you are suffering from," promises some possibility of improvement. In providing a meaningful diagnosis, the doctor encourages a placebo effect. To deliberately prescribe a useless placebo to a patient is unethical, but it is most certainly ethical for a doctor to have a positive message, to accompany legitimate treatment with compassion and to provide meaning for a patient's suffering.

We ³⁵ interviewed 76 patients consulting their general practitioner who had IBS by the Rome I criteria. Half of them were afraid that they might have intestinal cancer (Table 2). Most were given no diagnosis by their doctor and only 29 percent of them were reassured following their visit. Paradoxically, just 27 percent of those who had an organic diagnosis were worried about serious disease. They knew their diagnosis! When ill, people need some explanation or meaning for their suffering. Diagnosis can help provide that meaning.

Conclusion

The placebo effect, not the placebo, may occur in any therapeutic encounter, and can enhance any therapy. A bad doctor/patient interaction may have a nocebo effect. For the FGID, as for other disorders, these effects have important implications for medical practice. First, since ill people feel better just seeing a doctor, and tend to improve in time, doctors should strive to create and practice evidence-based medicine. Failing to do so risks the perpetuation of useless, often costly and sometimes harmful treatments and tests. Secondly, the placebo effect underlies the "art of medicine", and doctors should employ it maximally and ethically for the benefit of the sick. Particularly for the FGIDs, physicians through compassion and reassurance should seek to enhance this important, but oft-neglected component of medical care. This takes time.

urance should seek to enhance this important, but oft-neglected component of medical care. This takes time.

Time

"You can't see, touch, smell, or taste it, but we spend tens of millions of dollars on it every year. To many patients and physicians it is precious, maybe the most precious of all medical resources."

Frank Davidoff 1997 ³⁶

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**APPROACH TO THE PATIENT WITH
FUNCTIONAL GASTROINTESTINAL DISORDERS**

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PRESIDENTE Professor Enrico S. Corazziari

Coordinatore Emanuela Crescini

PROGRAMMA

VENERDÌ 24 SETTEMBRE 2010

- 11.30 - 13.25** REGISTRAZIONE PARTECIPANTI / ECM
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Presidente Alvaro D, Roma - *Moderatore* Pace F, Sierate
- 13.30 - 14.05** ❖ **DISFAGIA MOTORIA E FUNZIONALE**
- Presentazione clinica e questionario sintomatologico Covotta F, Roma
- Algoritmo diagnostico e Terapia Habib FI, Roma
Discussione
- 14.05 - 14.40** ❖ **BOLO FARINGEO**
- Presentazione clinica e questionario sintomatologico Cicerone C, Roma
- Algoritmo diagnostico e Terapia Piretta L, Roma
Discussione
- 14.40 - 15.15** ❖ **INCONTINENZA FECALE**
- Presentazione clinica e questionario sintomatologico Candeloro L, Roma
- Algoritmo diagnostico e Terapia Indinnimeo M, Roma
Discussione
- 15.15 - 15.50** ❖ **DOLORE ANORETTALE CRONICO**
- Presentazione clinica e questionario sintomatologico Candeloro L, Roma
- Algoritmo diagnostico e Terapia Corsetti M, Milano
Discussione
- 15.50 - 17.05** ❖ **MALATTIA DA REFLUSSO GASTROESOFAGEO**
- Presentazione clinica e questionario sintomatologico Cenani E, Roma
- Piroisi: Algoritmo diagnostico Cicala M, Roma
- Terapia Baldi F, Bologna
- Nell'infanzia Cucchiara S, Roma
Discussione
Presidente Angelico M, Roma - *Moderatore* Cuomo R, Napoli
- 17.45 - 18.45** ❖ **DISPEPSIA FUNZIONALE**
- Presentazione clinica e questionario sintomatologico Vincoli G, Roma
- Dolore epigastrico e Fastidio postprandiale: Algoritmi diagnostici Pallotta N, Roma
- Terapia Annibale B, Roma
Discussione
- 18.45 - 20.30** ❖ **NUOVI CONCETTI DI FISIOPATOLOGIA DELLE MALATTIE FUNZIONALI GASTROINTESTINALI**
Moderatore Barbara G, Bologna
- Introduzione Barbara G, Bologna
- Chemosensibilità intestinale, nervi, cellule enteroendocrine e recettori del gusto De Giorgio R, Bologna
- Alterazioni dell'innervazione nitrgerica. Risultati da culture di neuroni e delle cellule enterogliai Sarnelli G, Napoli
- Il ruolo della muscolatura intestinale nelle interazioni tra microorganismi e ospite Severi C, Roma
- Ruolo dell'infiammazione nelle malattie funzionali intestinali Desreumaux P, Lille, France
Discussione
- 20.30 - 21.00** ❖ **CONCLUSIONI / ECM** Corazziari ES, Roma

SABATO 25 SETTEMBRE 2010

- 07.30 - 08.25** REGISTRAZIONE PARTECIPANTI / ECM
- 08.25 - 08.30** ❖ **INTRODUZIONE** Corazziari ES, Roma
Moderatore Vernia P, Roma
- 08.30 - 09.05** ❖ **DOLORE E DISTENSIONE ADDOMINALE CRONICI**
- Presentazione clinica e questionario sintomatologico Ciccantelli B, Roma
- Algoritmo diagnostico e Terapia Basilisco G, Milano
Discussione
- 09.05 - 09.40** ❖ **SINDROME INTESTINO IRRITABILE (SII)**
- Presentazione clinica e questionario sintomatologico Cantarini R, Roma
- Dolore addominale con alterazioni dell'alvo: Algoritmo diagnostico Stanghellini V, Bologna
Discussione
- 09.40 - 10.15** ❖ **DIARREA FUNZIONALE**
- Presentazione clinica e questionario sintomatologico Cantarini R, Roma
- Diarrea: Algoritmo diagnostico Gasbarrini A, Roma
Discussione
Presidente Violi F, Roma
- 10.45 - 12.40** ❖ **VIVERE CON, E TERAPIA DEI, DISTURBI FUNZIONALI INTESTINALI**
Tavola Rotonda - Dieta, Acqua, Alimenti funzionali: Suggestioni o evidenze? Corazziari ES, Roma - Cuomo R, Napoli - Pace F, Sierate
- Fibre Bazzocchi G, Imola
Discussione
- PROBIOTICI**
Moderatore Corazziari ES, Roma
- Quali e per quali indicazioni? Corazziari ES, Roma
- Ecologia microbica nella sindrome dell'intestino irritabile Morelli L, Piacenza
- Esperienze cliniche Corazziari ES, Roma
- Esperienze dalle IBD Rizzello F, Bologna
- Esperienze dalla Pediatria Staiano A, Napoli
Discussione
- 12.40 - 13.10** ❖ **RILEVANZA DEI DISTURBI FUNZIONALI INTESTINALI IN MEDICINA GENERALE**
Ubaldi E, San Benedetto del Tronto
Discussione
Presidente Attili AF, Roma - *Moderatore* Corazziari ES, Roma
- 14.10 - 16.00** ❖ **STIPSIS FUNZIONALE**
- Presentazione clinica e questionario sintomatologico Biviano I, Roma
- Stipsi funzionale e refrattaria: Algoritmo diagnostico Bassotti G, Perugia
- Nell'infanzia Staiano A, Napoli
- Terapia Farmacologica nella stipsi Badiali D, Roma
- Terapia psicologica Biondi M - Tarsitani L - Piacentino D, Roma
- Terapia Chirurgica La Torre F, Roma
Discussione
- 16.00 - 16.30** ❖ **CONCLUSIONI / ECM** Corazziari ES, Roma

FACULTY

Alvaro D, Angelico M, Annibale B, Attili AF, Badiali D, Baldi F, Barbara G, Basilisco G, Bassotti G, Bazzocchi G, Biondi M, Cicala M, Corazziari ES, Corsetti M, Cucchiara S, Cuomo R, Desreumaux P, De Giorgio R, Gasbarrini A, Habib FI, Indinnimeo M, La Torre F, Morelli L, Pace F, Pallotta N, Piacentino D, Piretta L, Rizzello F, Sarnelli G, Severi C, Staiano AM, Stanghellini V, Tarsitani L, Ubaldi E, Vernia P, Violi F

Partecipano alle presentazioni Medici Specializzandi ed Interni afferenti alla Scuola di Specializzazione in Gastroenterologia dell'Università di Roma SAPIENZA

Biviano I, Candeloro L, Cantarini R, Cenani E, Ciccantelli B, Cicerone C, Covotta F, Vincoli G

ECM due percorsi formativi per Medico Chirurgo. Per entrambi i percorsi formativi

- *Specialisti* Gastroenterologi, Medicina Interna, Pediatri, Scienza dell'Alimentazione e Dietetica
- Medici di Medicina Generale
- Pediatri di Base (Pediatri di libera scelta)

24.09.2010 evento n. 6958-10025897 Percorso Formativo 1 [7 ore] LE MALATTIE FUNZIONALI GASTROINTESTINALI

25.09.2010 evento n. 6958-10028585 Percorso Formativo 2 [6 ore] LE MALATTIE FUNZIONALI INTESTINALI

Le malattie funzionali gastrointestinali comprendono condizioni ad alta prevalenza quali la sindrome dell'intestino irritabile, la stipsi cronica, l'incontinenza fecale, la dispepsia, la malattia da reflusso gastroesofageo, e costituiscono, dopo i disturbi osteoarticolari, la maggiore causa di richiesta di assistenza sanitaria. Per la mancanza di un marker biologico che le identifichi e per l'incertezza della loro fisiopatologia, le malattie funzionali sono diagnosticabili esclusivamente per i sintomi di presentazione. A tutt'oggi, tuttavia, mancano percorsi diagnostici standardizzati che, partendo dai sintomi, consentano un facile inquadramento di questi disturbi.

Il programma intende diffondere e mettere a disposizione dei medici italiani tre strumenti che facilitino nella diagnosi e nella gestione terapeutica dei pazienti con malattie funzionali gastrointestinali.

- Il primo strumento sono i criteri diagnostici sintomatologici di Roma che permettono di identificare i pazienti in maniera standardizzata e quindi condivisa.
- Il secondo strumento è un questionario, anch'esso standardizzato a livello internazionale che permette con poche domande anamnestiche e, in breve tempo, di inquadrare clinicamente il paziente.
- Il terzo strumento è un pacchetto di algoritmi diagnostici ognuno dei quali, elaborato dai maggiori esperti internazionali sulle evidenze scientifiche disponibili, è un percorso guidato che indica ed accompagna il medico per tappe successive partendo dal sintomo o sindrome con cui si presenta il paziente fino alla diagnosi e alla terapia.

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RINGRAZIAMENTI

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