choices; this may be an area of research that deserves further attention. Standardisation of both the technique and parameters and validation of software required for reducing the analysis time are first necessary to further increase clinical application. Finally, the exact role of pH-impedance monitoring will depend on its diagnostic relevance and ability to influence the management of GORD patients, particularly those with predominant extra-oesophageal symptoms. Data from Mainie and colleagues[18] and other groups concerning the outcome of surgery in PPI resistant patients that are carefully selected on the basis of objective impedance-pH analysis is eagerly awaited. Application of this recent technology will be particularly relevant to the pharmacological assessment of new drugs aimed at reduction of transient lower oesophageal relaxations, such as GABA-b agonists and glutamate ligands.[23–25]

In conclusion, at its present stage of development, impedance-pH monitoring represents a useful tool for studies and clinical research in oesophageal disorders. It is probably too early for it to be considered as ready for routine clinical application but recent studies hold promise, particularly for the group of patients dissatisfied with their anti-reflux treatment. Further studies should more directly measure the impact of results on patient management.

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Neurogastroenterology

Hypnosis for non-cardiac chest pain

O S Palsson, W E Whitehead

Hypnosis may be an effective treatment for patients with non-cardiac chest pain that has not responded to acid inhibition

Non-cardiac chest pain (NCCP) is a condition defined by recurrent episodes of substernal chest pain suggestive of coronary artery disease in patients in whom no cardiac cause can be found after a comprehensive evaluation.[1] It is aetiologically heterogeneous, and the cause in individual patients often remains unclear even after thorough investigation. Patients with NCCP are frequently not reassured by negative investigations and are persistent in their pursuit of further medical evaluations for possible cardiovascular disease. The consequent impairment in personal and occupational functioning and subjective well being can be substantial. A recent estimate places the annual cost of health care services provided in the USA to treat NCCP at 6.5 billion dollars.[2]

The most commonly identified cause of NCCP symptoms is gastro-oesophageal reflux disease. Consequently, a therapeutic trial of a proton pump inhibitor is often recommended to confirm the diagnosis and as the firstline treatment.[3 4] However, a variety of other factors have been suggested as possible causes of NCCP in individual patients, including oesophageal dysmotility, visceral hyperalgesia, musculoskeletal problems, and psychological factors, such as anxiety and somatisation.[5] When

patients fail to respond to proton pump inhibitors, few treatment options remain and the results of medical management are often unsatisfactory.

In this issue of *Gut*, Jones and colleagues[6] demonstrated in a small randomised controlled trial that hypnosis is an effective treatment for patients with NCCP that has not responded to acid inhibition ***(see page 1403)***. Following 12 sessions of individualised treatment with hypnosis, 80% of NCCP patients reported that they were ''completely better'' or ''moderately better'' compared with only 23% of patients in a control group. The controls received supportive psychotherapy and a placebo tablet to insure that the findings were not explained by expectancy or increased attention from a health care provider. The greater effectiveness of hypnotherapy was confirmed by the secondary endpoints in this study: hypnotherapy patients, when compared with control patients, showed greater reductions in pain intensity, greater improvements in quality of life, and greater reductions in medication usage. Strengths of this trial were the use of blind raters and an intent to treat analysis to evaluate efficacy.

The Manchester team that conducted this trial, headed by Dr Peter Whorwell, pioneered hypnosis treatment for functional gastrointestinal disorders more than two decades ago, and the current study is but the latest in a series of innovative contributions they have made over the years. They were the first to demonstrate that hypnosis can be of substantial help for refractory irritable bowel syndrome (IBS).[7 8] They went on to demonstrate in a large patient series that it is reliably effective for IBS, benefiting more than 70% of treated patients, and that the results last for years.[9 10] More recently, the Manchester group published a randomised placebo controlled trial in patients with functional dyspepsia showing that hypnotherapy is more effective than supportive therapy plus placebo medication or treatment with ranitidine.[11] In this study, they also demonstrated significant reductions in overall health care visits and amount of prescribed medication taken during the year following treatment with hypnosis, showing that the greater cost of treating patients with hypnosis is offset by downstream reductions in health care utilisation. The published studies of the Manchester group have inspired other research groups to test the effectiveness of hypnosis and to independently confirm the value of this type of treatment for severe and refractory IBS cases.[12] Replication of their work on functional dyspepsia is awaited.

Examining the similarities among the functional gastrointestinal disorders for which hypnosis has been found to be effective may provide insights into how hypnosis benefits these patients and how it might be adapted to further improve its efficacy. Each of these disorders is associated with a greater than expected amount of psychological symptoms,[13–15] and because hypnosis is a psychological intervention, it might be anticipated that it would be more effective in psychologically distressed patients. Consistent with this hypothesis, four published studies that evaluated the efficacy of cognitive behavioural therapy (CBT) for NCCP[16–19] all reported significantly greater improvement in the CBT condition compared with a control condition. However, these were uniformly small studies, and all of them compared CBT to no treatment or to standard care. Such control conditions do not elicit any anticipation of therapeutic change and therefore do not control for the placebo effect. (In this regard, the design of Jones *et al*'s trial is substantially stronger as its double placebo control condition is likely to have produced a considerable expectation of therapeutic effect.) However, psychological distress does not appear to be the explanation for the effectiveness of hypnosis. Unlike other psychological treatments, the benefits of hypnosis, at least in IBS where this has been tested, are no better in patients with anxiety and depression.[9] Thus hypnosis does not appear to be effective because it reduces psychological distress.

A second similarity between IBS, functional dyspepsia, and NCCP which may make them more amenable to treatment with hypnosis is that all three are defined by symptoms of pain or discomfort, and large subsets of patients with all three disorders have been shown to have lower thresholds for pain induced by intraluminal distension (that is, increased pain sensitivity).[20–22] While this has been interpreted by some as evidence of a biologically based difference in peripheral receptor sensitivity or spinal cord transmission of pain,[23] possibly related to inflammatory processes,[24] other evidence suggests that psychologically based perceptual response bias may explain the phenomenon[20 25]; when techniques that distinguish between biologically based pain sensitivity and perceptual response bias (that is, psychological influences on perception) are used, it has been shown for both IBS[25] and NCCP[26] that perceptual sensitivity is similar between patients and healthy controls but that psychologically based perceptual response bias is greater in patients and is correlated with pain thresholds. This suggests that patients with IBS and NCCP, and probably also functional dyspepsia,[27] are hypervigilant in noticing pain related sensations and interpreting them as symptoms of disease. This perceptual response bias may account for the fact that these functional gastrointestinal disorders are associated with multiple comorbid complaints. Whorwell's group have reported that hypnosis reduces pain sensitivity in IBS patients whose pain thresholds are abnormally low,[28 29] and research from our laboratory[30] shows that hypnosis substantially reduces somatisation in IBS patients. These findings suggest that hypnosis is perhaps uniquely able to modify hypervigilance for visceral pain sensations, and this may be one of the mechanisms that explains its effectiveness in functional gastrointestinal disorders.

A third similarity between IBS, functional dyspepsia, and NCCP is that all are symptom based diagnoses for which there are no biological markers. In each case, diagnosis requires the presence of a characteristic set of symptoms but also a negative medical evaluation for other diseases that might produce these symptoms.[31] Absence of objective criteria for diagnosis may increase uncertainty on the part of both the physician and the patient, with the result that anxiety and hypervigilance to symptoms on the part of either of them may play a greater role in the perpetuation of symptoms than might be the case, for example, in a fracture or an infection. One reason for the effectiveness of hypnosis intervention for functional gastrointestinal disorders could be that it focuses on reducing catastrophising cognitions and overattention to symptoms, which is likely to be particularly important in these symptom based conditions. This speculation requires testing.

This first ever study of hypnosis for NCCP has limitations which readers will need to keep in mind. Firstly, the 28 patients who were enrolled in the study were highly selected and may not be representative of all patients with NCCP: 865 patients were considered for the study, but 97% were not enrolled in treatment either because they were found to be ineligible (35%), could not be contacted (11%), listed travel related inconvenience or family and work conflicts (30%), or refused (20%). A second limitation to the study is that there was no follow up. Previous work from this group of investigators has shown that hypnosis produces improvements in IBS symptoms that are sustained for at least five years[9 10] and improvements in functional dyspepsia that persist for at least a year.[11] These durable treatment effects, and the reductions in health care visits

and medication use that accompanied treatment for functional dyspepsia,[11] are important to assess in NCCP.

IMPLICATIONS FOR TREATMENT OF NCCP WITH HYPNOSIS

Should further studies on hypnosis treatment for NCCP show equally dramatic beneficial effects of hypnosis, and especially if the long term benefits prove favourable, there is little question that hypnosis has much to offer chronic patients with this diagnosis. It must be acknowledged however that several obstacles presently prevent widespread practical application of hypnosis for gastrointestinal problems. Firstly, the number of health care providers trained in hypnosis is limited. Knowledge in a special gut directed approach to hypnosis, rather than general hypnotherapy, is required for good success in treating gastrointestinal disorders, and training in this method is hard to come by. Efforts to overcome this barrier include the development of gut focused hypnosis scripts which make it easier for health care providers to learn how to deliver effective treatment.[32]

A second barrier is that this approach to treatment is costly and requires multiple visits; this may deter use of this adjunctive treatment option. There are ongoing research studies to determine whether self hypnosis with the use of tape recordings may be equally effective.[33]

Finally, scepticism by some patients (and some physicians) due to lack of face validity of using a psychological therapy to treat a gut problem, especially a psychological method that has traditionally carried an aura of magic and mystery, may deter the treatment. However, educational efforts and growing interest due to the accumulating body of research indicative of the effectiveness of hypnosis treatment for functional gastrointestinal disorders are resulting in more and more patients and physicians becoming interested in hypnosis as a reasonable treatment alternative for refractory functional gastrointestinal symptoms, and increasing numbers of medical and mental health professionals are attending training workshops in gut directed hypnosis. For example, in the USA, several hundred clinicians nationwide now offer hypnosis treatment specifically for IBS, according to an empirically tested protocol.[32]

Much still remains to be done to enable patients with functional gastrointestinal disorders to benefit from hypnotherapy as a matter of course. Two changes in the way healthcare systems currently care for patients with these disorders will be important in this regard. One is the formal addition of hypnotherapy services to the scope of clinical services offered to patients seen in gastroenterology and primary care settings where functional gastrointestinal patients are treated, either through an established referral mechanism or preferably with on site delivery of hypnotherapy in medical clinics. Dr Whorwell and colleagues have convincingly demonstrated, through the example of their own clinic in Manchester,[9 10] that hypnotherapy can be incorporated successfully into clinical gastroenterology. For many years, they have employed several full time hypnotherapists (non-physicians) who routinely treat those of their functional gastrointestinal patients who prove unresponsive to more conventional treatment. They report a high rate of success in patients who in many other gastrointestinal settings would be left without further treatment options. While the integration of psychological services into ambulatory care clinics would seem optimal in light of the complex biopsychosocial nature of NCCP and other functional gastrointestinal disorders, it is a rare exception in today's healthcare delivery.

The other system change required for hypnosis to enter mainstream healthcare for gastrointestinal problems is improved coverage of the cost of hypnosis by health care systems or insurance providers. Such coverage seems reasonable in light of the accumulating evidence that hypnotherapy reduces healthcare utilisation and medication needs long term.[11] As long as this expense must be borne by the patients, as is predominantly the case in the USA and in some other countries, individuals with chronic functional gastrointestinal disorders will be deprived of the potential benefit of this treatment option.

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Colorectal cancer

Another important function for an old friend! The role of iron in colorectal carcinogenesis

J R Butterworth

Epidemiological data strongly support a role for dietary and haem iron in colorectal carcinogenesis through multiple pathways

The aetiopathogenesis of colorectal carcinoma (CRC) remains the holy grail for researchers in the field. CRC arises from benign neoplasms and evolves into adenocarcinoma through a stepwise histological progression sequence, proceeding from either adenomas or hyperplastic polyps/serrated adenomas. Genetic alterations are associated with specific steps in this polyp-adenocarcinoma sequence and are believed to drive the histological progression towards colon cancer. Approximately 50% of CRCs are attributed to dietary factors and about 15–20% to genetic factors, including the high risk familial syndromes.[1] Large prospectively collected epidemiological data have suggested that iron may confer an increased risk for CRC.[2]

WHAT ARE THE MECHANISMS BY WHICH IRON CONFERS AN INCREASED RISK OF CRC?

An apparent dose-response for serum ferritin level and adenoma risk suggests that exposure to dietary iron may be involved in the development of colorectal adenomas (and particularly proximal adenomas).[3] Dietary haem iron (through its effect on epithelial proliferation) is associated with an increased risk of proximal colon cancer, especially in women who drink alcohol.[4] In the dextran sodium sulphate model of mouse colitis, a twofold increase in dietary iron increased iron accumulation in colonic luminal contents at the colonic mucosal surface and in superficial epithelial cells with a concomitant increase in colitis associated CRC incidence.[5] High dietary iron decreases tocopherol levels in rat colonocytes, promotes oxidative stress (through generation of lipid peroxides and reactive oxygen species (ROS)) in faeces and colonocytes,[6–8] and decreases the activity of the colonic antioxidant enzyme manganese superoxide dismutase.[9] ROS activation of activator protein 1 and nuclear factor κB signal transduction pathways leads to transcription of genes involved in cell growth regulatory pathways.[10]

In addition, some studies suggest that possession of HFE gene mutations are statistically associated with increased rates of CRC,[11] but other studies have not confirmed this finding[12] Dietary haem also promotes the development of aberrant crypt foci (ACF),[13] the earliest identifiable neoplastic lesions in the colon cancer model. However, only a small fraction of ACF evolves to form cancer.[14] Progression from ACF through adenomatous polyp to cancer results from an accumulation of proteomic abnormalities (for example, B-catenin, E-cadherin, inducible nitric oxide synthase, cyclooxygenase (COX-2), and P16(INK4a)); genetic mutations (for example, K-ras, APC, p53); genomic instabilities; microsatellite instability; loss of heterozygosity; and defects in mismatch repair systems.

In summary, dietary iron is taken up by colon cells and participates in the induction of oxidative DNA damage. Its capacity to catalyse the formation of reactive oxygen species is an important risk factor for CRC.

Work conducted by Brookes and colleagues[15] in this issue of *Gut* begins to shed some light on a putative role of iron and the iron cognate proteins in colon carcinogenesis ***(see page 1449)***. Since identification of the HFE gene by Feder *et al* in 1996,[16] the last 10 years has seen has an unprecedented advance in our understanding of iron physiology. A number of iron related proteins have been identified and their role characterised.[17] Brookes and colleagues[15] have shown that ''progression to colorectal cancer is associated with increased expression in iron import proteins and a block in iron export due to decreased expression and aberrant localisation of *HEPH* (hephaestin) and FPN (ferroportin-1) respectively, resulting in increased intracellular iron which may induce proliferation and repress cell adhesion''.

A major finding of the study was that a difference in the expression of the iron related proteins appeared to be evident only at the carcinoma stage of epithelial cell dedifferentiation. Intuitively, if iron is related to the process of colorectal carcinogenesis then one would have expected to find a gradation of abnormalities from normal colorectal mucosa through dysplasia to carcinoma. However, there was no statistically significant difference between expression of the iron cognate proteins in normal tissue compared with colorectal adenomas with histological high grade dysplasia. It could be inferred from this that expression of these iron proteins is merely an epiphenomena related to accumulation of multiple genetic abnormalities but that iron itself is not involved in any meaningful aetiopathological manner to the process of colorectal carcinogenesis. However, would this be a correct interpretation?

There are a number of pathways by which iron may be involved in epithelial