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DO HORSES GET IRRITABLE BOWEL SYNDROME?

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ABSTRACT

Irritable bowel syndrome in man is not a single entity but has several causes. One of the most common forms has similarities with colic and laminitis in horses. Undigested food residues may pass from the small intestine into the colon where bacterial fermentation produces chemicals that lead to disease. In equines the consequences may be disastrous, but in healthy man, such malabsorption may not be harmful. After events such as bacterial gastroenteritis or antibiotic treatment, an imbalance of the colonic microflora with overgrowth of facultative anaerobes may arise which leads to malfermentation and IBS. It is not known whether such subtle changes may likewise be present in the microflora of equines who are susceptible to colic and laminitis. Metabolomic studies of urine and faeces may provide a suitable way forward to identify such changes in the horses gut and thus help to identify more accurately those at risk and to provide opportunities for the development of improved treatment.

INTRODUCTION

Do horses suffer from irritable bowel syndrome (IBS)? *Hudson & Merritt* (*2008)* suggest that idea is 'plausible'. Horses are of course creatures of habit and a simple change of routine, such as a change in training gallops will be enough for many of the string to display dirty rumps. This however, is simply akin to the diarrhoea that humans may get before an important football match or an exam. IBS is much more painful, and much more persistent. Nevertheless, the time seems ripe to consider whether recent advances in the knowledge of human IBS have any relevance to equine veterinary medicine.

IRRITABLE BOWEL SYNDROME

IBS has long been a thorn in the side of human gastroenterologists *(Forbes & Hunter 2007).* Affected patients suffer recurrent abdominal pain accompanied by a change in bowel habit – either diarrhoea or constipation. These symptoms persist for months and years and indeed the diagnosis cannot be sustained until symptoms have been present for at least 12 weeks and other more serious diseases excluded.

Although IBS is extremely common - as many of 15% of the population is said to be affected at some time in their lives - management has been embarrassingly poor. Repeated investigations, including endoscopy and radiology, stool culture and blood analyses reveal no abnormalities. Many physicians hope that the relief that patients may enjoy on finding that their problems are not caused by serious illnesses such as cancer, or colitis, will be such that the symptoms may clear spontaneously, or at least that they may learn to live with them. Such treatment as is available, including antispasmodic drugs, antidiarrhoeals, anxiolytics and antidepressants is so unsuccessful that many patients with IBS seek relief elsewhere, contributing significantly to the many millions of pounds spent each year in Britain on alternative medicine.

During the past 25 years, however, the understanding of IBS has grown steadily and practical symptom relief, based on understanding of the pathophysiology, is now available for the majority of patients. This has involved considerable advances in our understanding of the bacterial flora of the lower gut. In view of the complexity, and the metabolic and nutritional importance of the colon in equines, possibly lessons learned from IBS in humans may be relevant to gastrointestinal diseases of the horse.

FOOD INTOLERANCE

The first ray of light in the understanding of IBS came with the demonstration that in many patients IBS was caused by food intolerance *(Alun Jones et al 1982, Nanda et al 1989).* In the original Cambridge study, 21 out of 25 successive patients with IBS agreed to follow a highly restricted diet of lamb, pears and rice for up to 2 weeks. In 14 symptoms cleared completely. These were then instructed to reintroduce other food items one by

one on a daily basis to see which provoked their original symptoms. All 14 were successful in building up an exclusion diet on which they remained asymptomatic. 11 of the 14 agreed to return for rigorous double-blind testing in which test and control foods were administered via naso-gastric tubes. The food intolerances were thus confirmed objectively, and it was further demonstrated that rectal prostaglandin E2 production not only increased after the active challenges, but also correlated significantly with changes in 24hr faecal weight. (*Alun Jones et al 1982*). The importance of food intolerance in IBS has now been confirmed by many workers (*eg Nanda et al 1989,Bentley et al 1983 , Parker et al 1995*) and long term follow-up has shown that patients remain well on their diets (*Hunter et al 1988*).

Increasing experience in the management of these cases allowed the identification of those foods which were most likely to cause symptoms. These included most cereals, (except rice), dairy products, eggs, citrus fruit, nuts, onions, potatoes and yeast. It was therefore possible to develop a much less restrictive exclusion diet for the treatment of IBS and abandon the previous, and much derided, 'lamb and pears' routine. It also proved possible to characterise those cases most likely to respond to diet on the basis of their symptoms (discussed *by*

Wiesner et al 2009) . It has further been found that low-fibre diets are just as effective as exclusion diets, and simpler for patients to follow (*Woolner and Kirby, 1995*). These developments have meant that it is now possible to set up dietitian-lead IBS clinics, where young patients (ie those unlikely to be at risk of colon cancer), who have symptoms suggestive of IBS, may, after initial negative screening by blood tests and stool culture for organic disease, be treated efficiently and quickly by dietitians alone, without the need for a preliminary medical consultation. Such a dietitian-lead clinic at Addenbrooke's Hospital in Cambridge now achieves 75% success in controlling the symptoms of IBS and has greatly reduced hospital waiting lists.

OTHER CAUSES OF IBS

Food intolerance is the cause of only 50% of cases of IBS. Another major cause, responsible for perhaps 20%, is air-swallowing (aerophagia).

This is similar to wind-sucking in horses, but with an important difference. Wind-sucking is deliberate behaviour in horses which crib and gulp down air. Air swallowing in man is involuntary, indeed sub-conscious. Gas colic in horses is well recognised sometimes to be caused by wind-sucking alone (*Hillyer et al 2002).* Aerophagia in man is mainly due to anxiety, which leads to rapid shallow breathing, sighing and repeated swallowing, causing abdominal distension, rumblings, gaseousness and pain (but rarely diarrhoea). Treatment by respiratory physiotherapists to promote relaxation and to teach slower, diaphragmatic breathing is usually highly effective. (*Hunter 2007*)

A further relatively common form (20%) of IBS has been labelled 'overload and overflow' *(Weisner et al 2009*).This presents with intermittent abdominal pain and diarrhoea, often leading to the incorrect prescription of anti-diarrhoeal drugs. In fact these patients can be shown to have a mild form of constipation. Although they may have their bowels open daily, the motions are small and hard, often with mucus, leading to a faecal build up in the colon which is usually palpable per abdomen. After a few days the overload reaches a critical stage at which - often after a stimulus such as a rich meal or stress – the bowel empties vigorously, producing painful spasms of diarrhoea.

There are obvious similarities between 'obstruction and overflow' and impaction colic, but in contrast to horses, IBS patients with this problem need more, rather than less, fibre in order to keep the bowel moving smoothly. Furthermore, these patients never run into the dangerous complications as seen in the horse, where the intestine is exquisitely sensitive, such as endotoxaemia, dehydration and hypovolaemic shock.

MECHANISM OF FOOD INTOLERANCE IN IBS

FOOD ALLERGY?

The demonstration of the links between food and IBS inevitably lead to claims that it was all 'food allergy' This is untrue. Classical allergy in man, as in the horse, is mediated by IgE antibodies to specific antigens producing a range of problems from skin disorders to pulmonary problems such as asthma in man and chronic obstructive pulmonary disease in horses. (*Lessof et al 1980 Eder et al 2001,*) Specific IgE antibodies can be demonstrated in the blood by radioallergoabsorbent (RAST) testing, or by injection of the allergen into the skin, where it may produce a wheal. Such testing is unhelpful in IBS, where IgE concentrations are usually normal (*Lessof et al 1980*) It follows that therapeutic measures to relieve such allergies are unhelpful in the management of IBS.

HYPOLACTASIA

Intolerance of dairy products is frequently discovered in patients with IBS. This has inevitably lead to speculation that the digestion of the milk sugar lactose by intestinal enzymes may be impaired. The activity of the neutral β-galactosidase necessary for this is high in all human children, but declines with maturity (as it

does in foals - *Dyer et al 2002*) so that dietary lactose may then precipitate digestive upsets. Caucasian individuals from Northern Europe are highly unusual in that in many the activity of this enzyme is retained in adult life, and milk thus remains a staple in the European adult diet.

Testing in Caucasian patients with IBS has shown approximately 25% to be deficient in β-galactosidase activity, which is many more than in the general population. The effectiveness of a low-lactose diet, however, proved very disappointing, with only 30% responding. Surprisingly, some patients who failed to respond to a low-lactose diet nevertheless later found symptom relief avoiding dairy products. (*Parker et al 2001*). It seems probable that such patients are upset by dairy fats. Cows milk was shown many years ago to be peculiarly indigestible in man as it forms a curd in the stomach, which is much greater than that from milk from goats, sheep or donkeys (asses' milk was very popular for 'invalids' in the sixteenth century) or, indeed from human breast milk itself. (*Drummond and Wilbraham 1959*). The digestive problems which may arise from fat and long chain triglycerides in particular, have been well demonstrated in relation to Crohn's Disease (*Middleton et al 1995, Shoda et al 1996*).This may be akin to the digestive upsets in horses when fed damaged fatty acids (*Frape 2004*).

COELIAC DISEASE

Coeliac disease or gluten-sensitive enteropathy, is a condition seen frequently but not exclusively in childhood which causes atrophy of the mucosa of the small intestine leading to diarrhoea and malabsorption. It is due to an immune response to a 33-amino acid polypeptide derived from gluten, the main protein in wheat, rye and barley. In persons with genetic susceptibility, this polypeptide is changed in configuration by the enzyme tissue transglutaminase (tTG) to fit the antigen-receptor groove in intestinal macrophages, leading to immunological mucosal damage and induction of tTG, so that increased quantities of this enzyme appear in the blood, forming the basis of a screening test. The diagnosis is confirmed by small-bowel biopsy, and the disease responds successfully to a gluten-free diet in 97% of cases. Such a condition is not known to occur in horses, although a gluten-sensitive enteropathy may occur in dogs.

The demonstration of intolerance to gluten-containing grains in many cases of IBS inevitably lead to the suggestion that these were really 'mild' cases of Coeliac disease. However, tTG levels in IBS are never raised, the small bowel biopsy is always normal and it is clearly a completely separate condition.

FERMENTATION IN THE COLON

The horse is a herbivore, but lacks the means to digest the structural carbohydrates (CHOs) of plants. A characteristic of all grazing animals is the adaptation of some part of the gut to accommodate fermentation of such CHOs by micro-organisms to release rich energy sources such as volatile fatty acids (VFAs) and lactate. In ruminants, this occurs in the stomach, but in equines, the colon.

Man is an omnivore, and, like the pig, has a gastrointestinal tract where the majority of nutrients are digested and absorbed in the small intestine. The human colon, whilst appearing very straightforward compared to the famous 'double horse-shoe' of the enormous equine colon, is nonetheless more complex than that of carnivores. It contains a complex microflora which is in many respects very similar to that of the horse, with up to 10^{12} organisms per gram of faeces, and as many as 400-500 separate strains and species of bacteria. Fungi and protozoa may also be present, but are believed to be relatively less important than in the horse. The fermentation processes which take place in the colons of the two species are nevertheless very similar. Short-chain fatty acids, especially acetate, proprionate and butyrate (the major nutrient for colonocytes) are produced. A range of potentially toxic agents such as bile-acids and carcinogens are broken down, and B and K vitamins are produced and absorbed. Fermentation gases, particularly hydrogen, methane and carbon dioxide are generated (*Stephen, 1985, Macfarlane and Macfarlane,1997*).

It is now appreciated that fermentation in the colon provides up to 15% of human energy requirements - which may seem insignificant when compared to the figure of 80% for the horse, but is now known to have considerable clinical significance.

It is very well known that excessive feeding of non-structural CHOs, whether hydrolysable CHO in grain concentrates, or rapidly fermentable CHO in pastures, increases the risk of laminitis and colic in the horse. The horse is unusual in that the amount of α-amylase in the pancreatic juice is quite low (only 5-6% of that in the pig (*Frape 2004*) and hence starch digestion in the small intestine is strictly limited, despite the abundance of small intestinal α-glucosidases which further digest the limit dextrins resulting from amylase activity.

A similar excess of poorly absorbed food components reaching the colon is now thought to be a factor in the food intolerance of IBS. It has been known for many years that a significant portion of human dietary starch, ranging from 2-20% according to the individual and the diet, escapes digestion and becomes available for microbial fermentation in the colon. (*Stephen et al 1983*). Fructans, for example, are easily fermented molecules comprised of chains of fructose moieties linked to glucose which are widespread in CHO foods and are virtually indigestible in the human small intestine. An Australian group has suggested that 'FODMAPs', or (Fermentable Oligo-,Di-,Monosaccharides And Polyols) are a group of compounds likely to be particularly relevant. (*Gibson and Shepherd ,2005*). However, this suggestion overlooks the crucial importance of gluten in producing starch malabsorption, even in healthy volunteers. (*Anderson et al 1981*)

It would appear, however, that healthy man differs markedly from the horse in that excess CHO arriving in the colon can be fermented by a normal gut flora with little, if any, difficulty. Increased fermentation of soluble CHO in the horse may lead to diarrhoea, massive production of D(-)lactate, death of Enterobacteria, and endotoxaemia leading to shock and even death. By contrast, French investigators intubated the caecum in healthy human volunteers and infused 50gm raw wheat starch. Although VFA and lactate production was much increased, and caecal pH fell, there was little ill-effect other than bloating. Diarrhoea did not occur. Fermentation products were quickly and effectively absorbed, and the volunteers came to no harm (*Flourie et al 1986).*

Nevertheless, it is well established that certain indigestible sugars, such as sorbitol, may precipitate symptoms in IBS, but not in healthy controls (*Rumessen and Gudmand-Hoyer, 1988*). The reason for this is believed to lie in the colonic microflora. There is now strong evidence that IBS may arise in previously normal individuals following events which have the potential to damage the microflora. The risk of development of IBS in the following year is increased nearly 12-fold (*Garcia Rodriguez and Ruigomez 1999*) and even a single course of antibiotics prescribed in general practice raises the risk 4-fold *(Maxwell et al 2002).*

To date, no pathogens have been detected in the colonic microflora in IBS, (although it is true that as only 60% of the flora can be characterised by current techniques, (*Manichanh et al 2006*) this possibility cannot yet be completely excluded). Nevertheless the microflora in IBS is not normal. The colon contains little oxygen and is populated largely by anaerobic organisms. In IBS, however, there is overgrowth of facultative anaerobes, that is, organisms which are usually aerobic, but which somehow survive in the anaerobic colon. These include Enterobacteria, as well as species such as *Proteus* and *Klebsiella*. After challenge with foods which provoke symptoms, their numbers may increase by as much as two orders of magnitude. (*Balsari et al 1982, Bayliss et al 1986)* There is also a significant reduction in *Lactobacilli* and *Bifidobacteria*.

The importance of this imbalance in causing abnormal colonic fermentation was demonstrated in a study in which IBS patients and age and sex-matched controls, were studied in a purpose built calorimeter which allowed the collection of excreted fermentation gases - hydrogen and methane. On a standard diet, patients excreted large quantities of hydrogen, but overall gas production was not significantly more than controls. When the subjects were retested after two weeks on an exclusion diet which had the same fibre content as the standard diet, there was little change in gas excretion in controls, but a dramatic fall in hydrogen in the patients, which was associated with improvement in symptoms.(Fig 1) That this was not due to changes in starch malabsorption alone was confirmed by the demonstration that breath hydrogen release in both IBS and

controls was significantly reduced on the exclusion diet after 20g of a non-absorbable sugar, lactulose. *(King et al 1998).*

Furthermore, similar change in gas excretion and improvement in symptoms of IBS in patients continuing a standard diet was seen after administration of antibiotics to reduce the metabolism of the colonic bacteria *(Dear et al 2005).*

Hydrogen is not the only chemical produced by the gut microflora in IBS. Metabolomic techniques, allowing analysis of complex chemical mixtures in biological fluids, have shown significant differences in a number of compounds in breath and urine in IBS patients, whose concentrations are reduced when patients follow the exclusion diets which control their symptoms.(Fig2)(*Bilbao Montoya 2007*). Similar results have also been recently reported in Crohn's disease and ulcerative colitis but using nuclear magnetic resonance (NMR). (*Williams et al 2009*). Such chemicals may give rise to diarrhoea and to increased pain on colonic distension, possibly by their effects on the enteric nervous system. However, colonic motility studies have been disappointing in understanding human IBS.

VETERINARY APPLICATIONS

Both IBS and equine colic (and laminitis) may represent the unfortunate effects of CHO passing undigested from the small bowel into the colon and being fermented by the microflora. Because of the extreme sensitivity of equines to lactic acidosis, these consequences are more severe for horses than for man. Diet is crucial to both conditions, although this can be controlled more readily in horses than in omnivorous man. Most thoroughbreds are on a carefully controlled exclusion diet.

It is presumptuous for a human physician to make suggestions about equine disorders. Much of the work on malfermentation in IBS has followed the leads given by studies on ruminants and equines, and to quote Alison Stephen (1985) 'it is clear that this is an area in which animal biochemists are far ahead in their thinking' One or two avenues, however, might be worth veterinary exploration.

Several studies on the epidemiology of colic have appeared in recent years and have identified a number of factors that are associated with increased risk of colic including parasite burden, certain feed types, recent

change in feeding practices, stabling, lack of access to pasture and water, previous attacks of colic, medical treatments, increasing exercise and transport. (*eg Goncalves et al 2002, Hillyer et al 2002*) (*Archer and Proudman 2006).* However, although the medical treatments may have included antibiotics, which are known to be able to disrupt the endogenous bacterial flora of the horse (*Papich 2003*), little attention appears to have been paid to possible differences in the composition of the colonic microflora.

Certainly, certain bacteria have been associated with colic. *Clostridium perfringens* and *C. difficile* have been implicated in the pathogenesis of some cases (*Weese et al 2001*) as well as *Salmonella* from silage. *(Frape 2004*) but these are all frank pathogens, in equines and in man. It has been claimed that no differences exist in the microbial microflora between normal ponies and those prone to laminitis, but this was based on a lack of differences in faecal vasoactive amine content after a fructans challenge, rather than microbiological studies.(*Crawford et al 2007*). The present author has been unable to discover any equine studies seeking more subtle changes in the microflora, as seen in human IBS. This is potentially very important, as not every horse fed excess grain develops colic or laminitis (*Lopes et al 2004*). Are variations in susceptibility to colic caused by genetic variation?. This seems unlikely in the highly in-bred TB. May not the nature of the gut flora be crucial? Interest in the role of the gut flora in human obesity and metabolic syndrome is growing rapidly *(Turnbaugh et al 2006, Kalliomaki M et al 2008*). The suggestion that laminitis in ponies has similarities to human metabolic syndrome (*Treiber et al 2006*) is another factor pointing towards the potential role of the microflora.

To quote *Hudson & Merritt (2008),* 'research initiatives between researchers in veterinary and human medicine are to be welcomed'. Metabolomics may offer an elegant way forward. Many compounds produced in the gut are absorbed into the body, and excreted on the breath or in the urine. Subsequent analysis by GC/MS or NMR and chemometrics may, as previously mentioned, reveal diagnostic differences. After initially exciting pilot studies (*Bilbao Montoya 2007, Williams et al 2009*) large scale human studies on the diagnostic potential of such techniques are now underway in the hope that they may lead to considerable advances-perhaps in the horse as well as man - in our understanding of what the present author has labelled 'enterometabolic disorders' *(Hunter 1991).*

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REFERENCES

Alun Jones V, McLaughlan P, Shorthouse M, Workman E and Hunter JO (1982) Food intolerance: a major factor in the pathogenesis of irritable bowel syndrome. *Lancet*,**ii**,1115-1117

Anderson IH, Levine AS, Levitt MD (1981) Incomplete absorption of the carbohydrate in all purpose wheat flour. *New England Journal of Medicine* **304**, 891-2

Archer T C Proudman C J (2006) Epidemiological clues to preventing colic *Veterinary Journal* **172** 29-39

Balsari A Ceccarelli A Dubini F et al The faecal microbial population in IBS *Microbiologica* 1982 **5** 189-94

Bayliss C E Bradley H K Alun Jones V Hunter J O (1986) Some aspects of colonic microbial activity in IBS associated with food intolerance Annals 1st Super Sanita Vol **22** 959-964

Bentley S J, Pearson D J, Rix K J B (1983) Food hypersensitivity in IBS *Lancet* **ii** 295-297

Bilbao Montoya M P *(2007*) An investigation into the effects of bacterial fermentation in Autism PdDThesis University of Cranfield

Crawford C Sepulveda M F Elliott J Harris P A Bailey S R (2007) Dietary fructan carbohydrate increases amine production in the equine large intestine: implications for pasture associated laminitis Journal of Animal Science **85** 2949-58

Dear K L E Elia M Hunter J O (2005) Do interventions which reduce colonic bacterial fermentation improve symptoms of IBS? *Digestive Diseases and sciences* **50** 758-766

Drummond J C and Wilbraham A (1959) *The Englishman's Food*. London: Jonathan Cape

Dyer J, Merediz EF-C, Salmon KSH, Proudman CJ, Edwards GB, and Shirazi-Beechey SP (2002) Molecular characteristics of carbohydrate digestion and absorption in equine small intestine. *Equine Veterinary Journal* **34**, 349-58

Eder C, Curik I, Brem G et al (2001) Influence of environmental and genetic factors on allergen-specific immunoglobulin-E levels in sera from Lipizzaner horses. *Equine Veterinary Journal* **33**, 714-20 .

Flourie B, Florent C, Jouany JP, Thiverd P, Etanchard F, Rambaud JC. (1986) Colonic metabolism of starch in healthy humans. Effect on fecal outputs and clinical symptoms *Gastroenterology* **90**, 111-119

Forbes A L Hunter J O (2007) Irritable Bowel Síndrome, Medicine **35** 267-71

Frape D (2004) *Equine Nutrition and Feeding*, (3rd edition).Oxford:Blackwell

Garcia Rodriguez L A, Ruigomez A (1999) Increased risk of IBS alter bacterial gastroenteritis- a cohort study. *British Medical Journal* Vol **318** 565-566

Gibson PR, Shepherd SJ. (2005) Personal view: food for thought – Western life-style and susceptibility to Crohn's Disease. The FODMAP hypothesis. *Alimentary Pharmacology and Therapeutics* **21**, 1399-1409

Goncalves S Juillard V Leblond A *(2002*) Risk factors associated with colic in horses *VetRes* **33** 641-52

Hillyer, MH, Taylor FG, Proudman CJ, Edwards GB, Smith JE, French NP. (2002) *Equine Veterinary Journal*, **34**, 455-63

Hudson N P H Merritt A M (2008) Equine Gastrointestinal motility research: Where we are and where we need to go *Equine Veterinary Journal* **40** 422-28

Hunter J O *(1991)* Food allergy – or enterometabolic disorder? *Lancet* **ii** 495-6

Hunter J O *(2007*) *Irritable Bowel Solutions*. Vermilion, London.

Hunter J O Workman E Alun Jones V (1988) IBS: dietary studies *Topics in Gastroenterology* Oxford Blackwell Scientific publications

Kalliomaki M Collado M C Salminen et al (2008) Early differences in faecal microbiota composition in children may predict overweight *American Journal of Clinical Nutrition* **87** 534-38

King T S Elia M Hunter J O Abnormal Colonic Fermentation in Irritable Bowel Syndrome *Lancet* 1998 **352** 187-9

Lessof MH, Wraight DG, Merrett TG, MerrettJ and Buisseret PD (1980) Food allergy and intolerance in 100 patients. *Quarterly Journal of Medicine* **195**, 259-271.

Lopes M A White M A Chrisman M V Ward D L *(2004)* Effects of large amounts of grain on colonic contents and faeces in horses *American Journal of Veterinary research* **65** 687-94

Macfarlane GT and Macfarlane S (1997) Human colonic microbiota: ecology physiology and metabolic potential of intestinal bacteria. *Scandinavian Journal of Gastroenterology Supplement* **222** 3-9

Manichanh C Rigottier-Gois L Bonnaud E et al *(2006)* Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach *Gut **55*** 205-11

Maxwell P R Rink E Kumar D Mendall M A Antibiotics increase functional abdominal symptoms *American Journal of Gastroenterology* 2002 **97** 104-108

Middleton S J Rucker J T Kirby G A et al (1995) Long-chain triglycerides reduce the efficacy of enteral feeds in patients with active Crohn's disease *Clinical Nutrition* **14** 229-236

Nanda R, James R, Smith H et al (1989) Food Intolerance and the Irritable bowel syndrome *Gut* **30** 1099-1104

Papich M G *(2003)*Antimicrobial therapy for gastrointestinal diseases ***V**et Clin North Am Equine Pract*; **19** 645-63

Parker T J, Naylor S J, Riordan A M et al (1995) Management of patients with food intolerance in Irritable Bowel syndrome the development and use of an exclusion diet *Journal of Human Nutrition and Dietetics* **8** 159-66

Parker J J Woolner J T Prevost A T et al (2001) IBS: is the search lactose intolerance justified? *European Journal of Gastroenterology and Hepatology* **13** 219-225

Rumessen J J Gudmand-Hoyer E (1988) Functional bowel disease: Malabsorption and abdominal distress after ingestion of fructose, sorbitol and fructose-sorbitol mixtures. *Gastroenterology* **95** 694-700

Shoda R Matsueda K Shigeru et al (1996) Epidemiologic analysis of Crohn's disease in Japan: Increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn's disease in Japan *American Journal of Clinical Nutrition* **63** 741-745

Stephen AM (1985) Effect of food on the intestinal microflora. In *Food and the Gut* (Hunter JO and Alun Jones V eds) London:Balliere Tindall

Stephen AM, Haddad AC, Phillips SF (1983) Passage of carbohydrate into the colon: direct measurements in humans. *Gastroenterology* **85**, 589-595

Turnbaugh P J Ley R E Mahowald M A et al *(2006)* An obesity-associated gut microbiome with increased capacity for energy harvest *Nature* **444** 1027-31

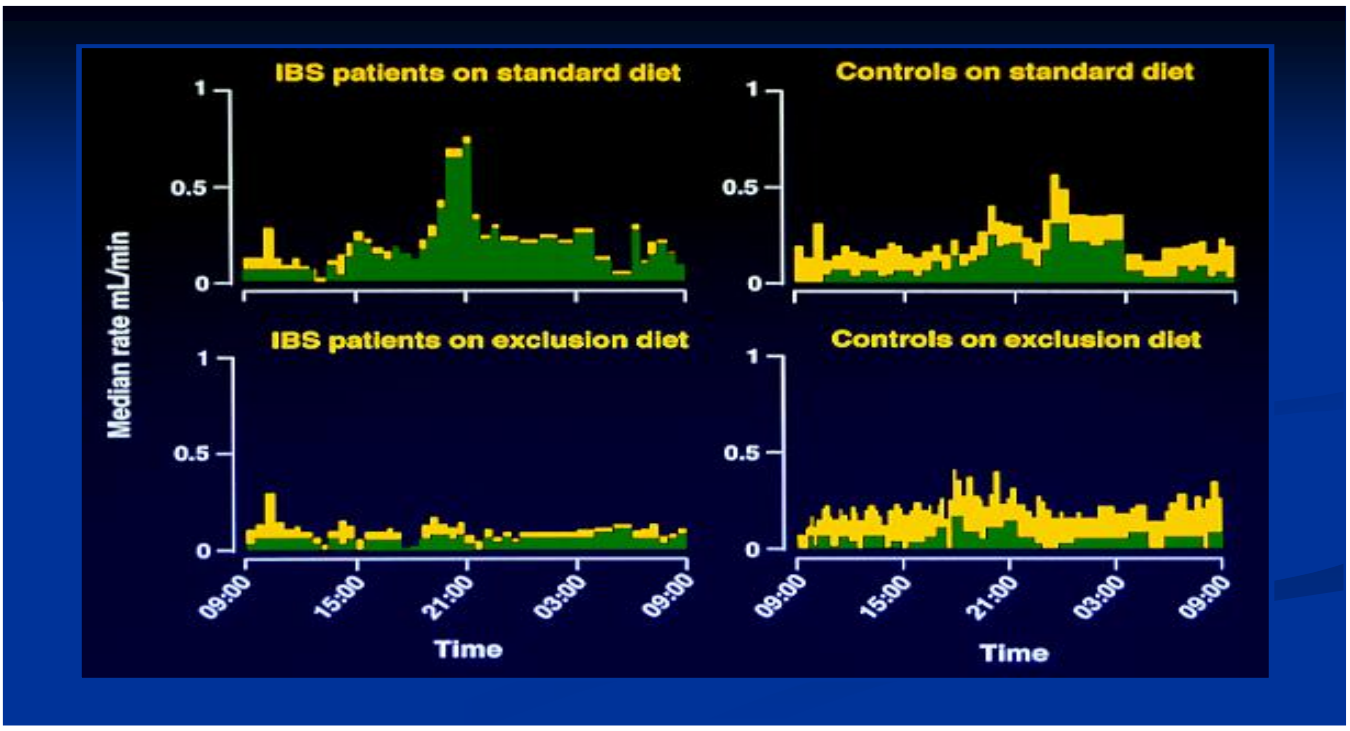
Weese J S Staempfli H R Prescott J F (2001) Prospective study of the roles of Clostridium difficile and enterotoxigenic clostridium perfringens in equine diarrhoea *Equine Veterinary Journal* **33** 403-409

Wiesner M, Naylor S J, Copping A, Furlong A, Lynch A G, Parkes M, Hunter J O (2009) Symptom Analysis in IBS as a guide to selection of treatment *Scandinavian Journal of Gastroenterology* **in press**

Williams H R T Cox I J Walker DG et al *(2009)* Characterization of Inflammatory Bowel Disease With Urinary Metabolic Profiling *Am J Gastroenterol* **104** 1435–1444

Woolner T J, Kirby G A, (2000) Clinical audit of the effects of low fibre diet on IBS *Journal of Human Nutrition and Dietetics* **13** 24-253

Fig 1



24hr excretion of hydrogen (Green) and methane (yellow) in patients with IBS and age and sex matched controls on standard and exclusion diets matched for fibre content. Reproduced by kind permission of Elsevier Edinburgh.

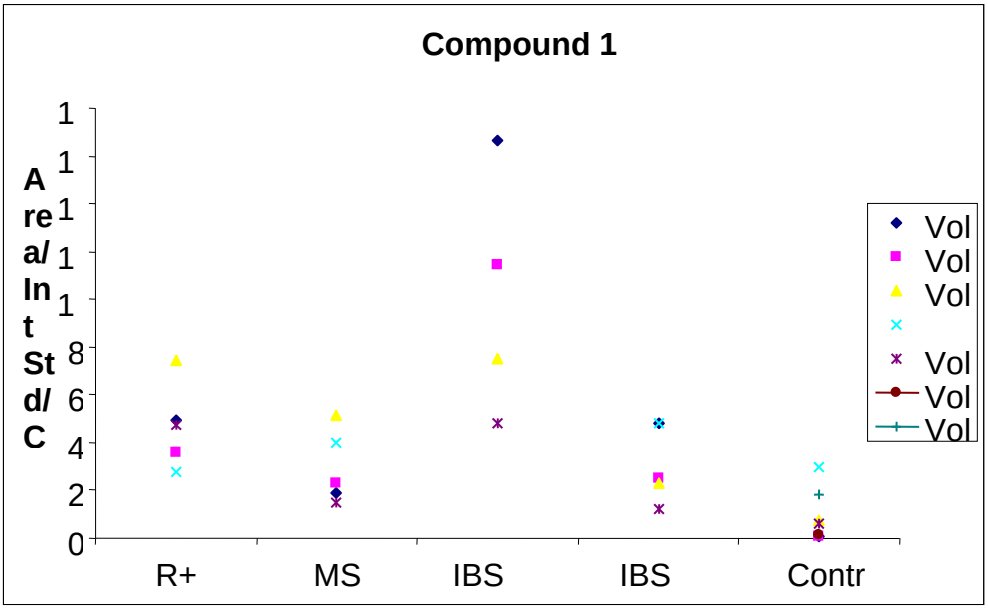


Fig 2 Excretion of 1,2-ethyl methyl benzodicarboxylic acid in the urine of patients with food intolerant IBS before and after diet and patients with other causes of abdominal pain. Excretion is significantly increased in the IBS group before diet and falls back to the control levels on treatment. Reproduced from Bilbao Montoya 2007 by kind permission of the author.