PostScript

LETTERS

If you have a burning desire to respond to a paper published in *Gut*, why not make use of our ''rapid response'' option?

Log onto our website (www.gutjnl.com), find the paper that interests you, and send your response via email by clicking on the ''eLetters'' option in the box at the top right hand corner.

Providing it isn't libellous or obscene, it will be posted within seven days. You can retrieve it by clicking on ''read eLetters'' on our homepage.

The editors will decide as before whether to also publish it in a future paper issue.

Ghrelin and *Helicobacter pylori*

We read with interest the article by Nwokolo *et al* reporting raised serum ghrelin levels following *Helicobacter pylori* eradication (Gut 2003;**52**:637–40). There are some exceptions to the interpretation of the data that we would take.

The authors state that the increase in ghrelin levels seen in their study ''lends support to the view that ghrelin could be involved in the long term regulation of body weight''. While there is growing evidence to support this in the literature,[1–3] this study does not present any such data and is not methodologically geared towards addressing this question. The proposal that eradication of *H pylori* leads to an increase in ghrelin levels, which in turn leads to an increase in obesity, is also without foundation. The only known situation in which hyper-ghrelinaemia is associated with obesity is in Prader-Willi syndrome.[4] In all other studies ghrelin levels correlate inversely with measures of body adiposity, and are altered in a compensatory manner by changes in body weight.[5] To suggest therefore that *H pylori* eradication leads to a hyper-ghrelinaemic state that drives increased appetite is not physiologically feasible as any transient appetite increase would be expected to be countered by any increase in adiposity, which in turn would suppress ghrelin levels.

The authors' proposal that ''children with *H pylori* may have relatively low ghrelin concentrations contributing to growth retardation'' is also without foundation. A recent study has shown *H pylori* status to have no effect on ghrelin levels.[6] The role of ghrelin on the growth of children remains unclear. Ghrelin is an endogenous ligand to the growth hormone secretagogue receptor (GHS-R), and potently stimulates growth hormone release. It may indeed have a role to play in growth, as in patients with a genetic growth hormone releasing hormone deficiency nocturnal enhancement of growth hormone secretion remains,[7] an effect that may be mediated by ghrelin.

One other proposal of the authors is that *H pylori* eradication increases 24 hour gastric acidity by a ghrelin dependent mechanism. While central and peripheral ghrelin administration has been shown to increase stomach acidity when given to rats,[8] data are lacking in humans. The small but statistically significant increase in acidity seen here would be expected after *H pylori* eradication, and is likely to be secondary to parietal cell recovery following resolution of inflammation. The suggestion that hypergastrinaemia leads to lower ghrelin levels, and vice versa, is not supported in the literature.[9]

C D R Murray, A V Emmanuel
St Mark's Hospital, Watford Road, Harrow, Middlesex, UK

Correspondence to: Dr C D R Murray; charlie.murray@talk21.com

References

1 **Cummings DE**, Weigle DS, Frayo RS, *et al*. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002;**346**:1623–30.
2 **Nakazato M**, Murakami N, Date Y, *et al*. A role for ghrelin in the central regulation of feeding. *Nature* 2001;**409**:194–8.
3 **Wren AM**, Seal LJ, Cohen MA, *et al*. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001;**86**:5992.
4 **Cummings DE**, Clement K, Purnell JQ, *et al*. Elevated plasma ghrelin levels in Prader Willi syndrome. *Nat Med* 2002;**8**:643–4.
5 **Hansen TK**, Dall R, Hosoda H, *et al*. Weight loss increases circulating levels of ghrelin in human obesity. *Clin Endocrinol (Oxf)* 2002;**56**:203–6.
6 **Gokcel A**, Gumurdulu Y, Kayaselcuk F, *et al*. Helicobacter pylori has no effect on plasma ghrelin levels. *Eur J Endocrinol* 2003;**148**:423–6.
7 **Maheshwari HG**, Pezzoli SS, Rahim A, *et al*. Pulsatile growth hormone secretion persists in genetic growth hormone-releasing hormone resistance. *Am J Physiol Endocrinol Metab* 2002;**282**:E943–51.
8 **Masuda Y**, Tanaka T, Inomata N, *et al*. Ghrelin stimulates gastric acid secretion and motility in rats. *Biochem Biophys Res Commun* 2000;**276**:905–8.
9 **Dornonville DLC**, Bjorkqvist M, Sandvik AK, *et al*. A-like cells in the rat stomach contain ghrelin and do not operate under gastrin control. *Regul Pept* 2001;**99**:141–50.

Authors' reply

We would like to draw the attention of Drs Murry and Emmanuel to the objectives set out clearly in the introductory section of our paper.

Our study was not designed to address the question of whether ghrelin is involved in long term regulation of body weight. Furthermore, the duration of the study was too short to see any change in body mass index. More importantly, waist circumference would be a better anthropometric measure of change in body fat composition supported by sequential dual energy *x* ray absorptiometry or magnetic resonance imaging. The results of our study were unexpected and there was nothing in the literature that gave us forewarning. We would have designed the study to follow up the subjects for at least one year, monitoring their plasma ghrelin, and assessing changes in body composition using the techniques described above.

The authors refer to ''physiological feasibility'' and thereby miss the point that *Helicobacter pylori* infected stomachs exhibit distortion of normal physiological mechanisms. For example, the tight reciprocal relationship between gastrin and intragastric acidity seen in *H pylori* negative subjects is modified in *H pylori* positive subjects. We believe that a *H pylori* infected stomach produces less ghrelin, leading to decreased appetite and food intake. The physiological response should be that the resulting weight loss leads to a compensatory increase in ghrelin, increased appetite, and weight gain, and so on. We believe that this ''physiological'' mechanism is altered by the presence of *H pylori*, possibly by resetting a putative ''ghrelin thermostat'' at a lower level, allowing thinness and hypoghrelinaemia to occur together. Proof will come only from further experimentation.

The authors cite a study comparing spot measurements of plasma ghrelin in women with and without *H pylori* gastritis;[1] this does not amount to a robust challenge to our hypothesis on *H pylori*, ghrelin, and children. The authors repeat the widely held although unproven belief that the increase in intragastric acidity after *H pylori* cure can be attributed to recovery of parietal cells from inflammation. They ignore our observation of a positive correlation between ghrelin and 24 hour intragastric acidity. We accept that the relationship between gastrin and ghrelin is unproven in humans but this emphasises the paucity of human data and the need for more studies.

C U Nwokolo, H Randeva
University Hospitals, Coventry and Warwickshire NHS Trust, Clifford Bridge Rd, Coventry CV2 2DX, UK

Correspondence to: Dr C U Nwokolo; chuka.nwokolo@uhcw.nhs.uk

Reference

1 **Gokcel A**, Gumurdulu Y, Kayaselcuk F, *et al*. Helicobacter pylori has no effect on plasma ghrelin levels. *Eur J Endocrinol* 2003;**148**:423–6.

Helicobacter pylori, ghrelin, and obesity

Nwokolo *et al* have demonstrated that following eradication of *Helicobacter pylori* from asymptomatic patients, plasma ghrelin ''increases profoundly'' (*Gut* 2003;**52**:637–40). Although we find these results interesting, we cannot agree with the conclusion that this may be causally linked to epidemiological observations of the rising incidence of obesity and oesophageal adenocarcinoma in Western populations. In particular, the present study in fact demonstrates that after *H pylori* eradication, ghrelin merely returns to levels detected in non-obese control patients using the same hormone assay.[1] It would seem likely that *H pylori* infection, leading to oxyntic gland atrophy,[2] is associated with at most a mild suppression of plasma ghrelin, which recovers after treatment. This seems unlikely to have a profound effect on calorie intake, particularly as obese patients have a lower mean plasma ghrelin concentration than matched non-obese controls.[1] While it is possible, although unproven, that the virtual abolition of plasma ghrelin seen after roux-en-Y gastric bypass surgery may contribute to the paradoxical reduction in hunger

observed in these patients, it is simplistic to suggest that the moderate reduction in ghrelin, as seen in the *H pylori* infected group in this study, is protective against the development of obesity and its associated conditions.

R C Macadam, V Borse, I Dodo, S G Pollard
St James' University Hospital, Level 8, Clinical Sciences Building, Leeds LS9 7TF, UK

Correspondence to: Mr R C Macadam; robert.macadam@btinternet.com

References

1 **Cummings D**, Weigle D, Frayo R, *et al*. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002;**346**:1623–9.
2 **Date Y**, Kojima M, Hosoda H, *et al*. Ghrelin, a novel growth hormone-releasing acylated peptide, is synthesized in a distinct endocrine cell type in the gastrointestinal tracts of rats and humans. *Endocrinology* 2000;**141**:4255–61.

Author's reply

Macadam *et al* have rightly questioned whether our novel observation is merely epiphenomenal or of pathophysiological significance. Their ''gut feeling'' is that it is the former as the changes are ''mild'' and ghrelin concentrations after *Helicobacter pylori* cure are no different from those seen in a non-obese Western population. They also suggest that the ''moderate'' reduction of ghrelin in *H pylori* positive subjects (which they attribute to oxyntic gland atrophy) is unlikely to protect these individuals from obesity.

There is no doubt that cure of *H pylori* increases plasma ghrelin in ''healthy subjects''. The real questions are: whether plasma ghrelin concentrations are higher in *H pylori* negative individuals and, if so, whether the higher ghrelin concentrations cause weight gain, and whether any weight gained exacerbates gastro-oesophageal acid reflux enough to induce Barrett's oesophagus and cancer. There are no satisfactory answers to these questions based on first class evidence but in our discussion, we considered some indirect evidence. Firstly, populations with a high prevalence of *H pylori* have a relatively high proportion of thin children and adults, and those with a low prevalence have a higher proportion of obese individuals; we acknowledge the numerous other confounding factors in our paper.

Secondly, Furuta *et al* showed that patients cured of *H pylori* gained weight.[1] Lane *et al*, continuing their reporting of the large Bristol *Helicobacter* project, showed that at the end of six months, individuals who received treatment for *H pylori* increased their weight by 0.6 kg over and above a matched group that received placebo.[2] Finally, in the only published study of its kind, infusion of ghrelin into healthy subjects was associated with increased appetite and food intake.[3]

In the presence of *H pylori*, abnormalities in the function of the gastric neuroendocrine cell population can be detected long before gastric atrophy occurs. ''Inappropriate'' hypergastrinaemia and disturbances in D cell function have been described; these are fully reversible, returning to normal soon after *H pylori* cure.[4 5] Similarly, gastric atrophy which is irreversible in the short term is unlikely to be the mechanism that mediates hypoghrelinaemia in *H pylori* positive subjects, given that reversion to normal non-obese concentrations occurred 6–12 weeks after cure, which was the time course of our study. Also, the median age of our subjects was 36 years; the fact that they had normal gastrin concentrations and 24 hour intragastric acidity makes it unlikely that they had significant gastric atrophy.

In general, single factors rarely account for large epidemiological trends. We do not believe that everything can be explained by ghrelin; that would really be simplistic. However, we believe that *H pylori* positive subjects with low ghrelin may have decreased appetite and food intake and are thinner than their *H pylori* negative counterparts in the Western world. Their poor nutritional status would be exaggerated by coexisting dyspepsia due to peptic ulceration, concurrent infection, and poor diet. They would have relatively lower intragastric acidity. Taken together, these factors could protect these individuals from gastro-oesophageal reflux disease (GORD). Conversely, having normal ghrelin, a good appetite, and normal intragastric acidity could make GORD more likely, possibly leading to Barrett's oesophagus and oesophageal adenocarcinoma.

C U Nwokolo, H Randeva
University Hospitals, Coventry and Warwickshire NHS Trust, Clifford Bridge Rd, Coventry CV2 2DX, UK

Correspondence to: Dr C U Nwokolo; chuka.nwokolo@uhcw.nhs.uk

References

1 **Furuta T**, Shirai N, Xiao F, *et al*. Effect of Helicobacter infection and its eradication on nutrition. *Aliment Pharmacol Ther* 2002;**4**:799–806.
2 **Lane A**, Harvey R, Murray L, *et al*. Effect of Helicobacter pylori eradication on body weight: the Bristol Helicobacter project. *Gastroenterology* 2003;**124**(suppl 1):A622.
3 **Wren A**, Seal L, Cohen M, *et al*. Ghrelin enhances appetite and increases food intake in humans. *J Clin Endocrinol Metab* 2001;**86**:5992.
4 **Smith J**, Pounder R, Nwokolo C, *et al*. Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with Helicobacter pylori. *Gut* 1990;**31**:522–5.
5 **Prewett E**, Smith J, Nwokolo C, *et al*. Eradication of Helicobacter pylori abolishes 24-hour hypergastrinaemia: a prospective study in healthy subjects. *Aliment Pharmacol Ther* 1991;**5**:283–90.

CORRECTION

In the paper by Feinle-Bisset *et al* (*Gut* 2003; **52**: 1414–18), an author was missing from the author list, listing only three of the authors as C Feinle-Bisset, B Meier and M Fried. In fact, there was a fourth co-author, C Beglinger, based at University Hospital Basle, Switzerland.

NOTICES

British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew's Place, London NW1 4LB. Email: bsg@mailbox.ulcc.ac.uk

Hong Kong-Shanghai International Liver Congress 2004

This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is ''Liver Diseases in the Post-Genomic Era''. Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4300/8101 2442; fax: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org

PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

This continuing medical education programme will take place on 19−20 March 2004 at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Further details: Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195. Tel: +1 410 955 2959; fax: +1 410 955 0807; email: cmenet@jhmi.edu; website: www.hopkinscme.org

39th Annual Meeting of the European Association for the Study of the Liver

This meeting will be held on 15–19 April 2004 in Berlin, Germany. Further details: Secretariat, c/o Kenes International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: info@easl.ch; website: www.easl.ch/easl2004

- Deadline for receipt of abstracts: 16 November 2003
- Deadline for early registration 10 February 2004

14th International Workshop of Digestive Endoscopy, Ultrasonography and Radiology

The 14th International Workshop of Digestive Endoscopy, Ultrasonography and Radiology will be held in Marseille on 27—28 May 2004. For further information, please contact: Nathalie Fontant, Atelier Phenix, 41 rue Docteur Morruci, 13006 — Marseille (tel: (33) 04-91-37-50-83; fax: (33) 04-91-57-15-28; e-mail: nfontant@aphenix.com).

International Hans Popper Award 2003

This year the International Hans Popper Award goes to Gut editorial board member, Professor Scott Laurence Friedman of the Mount Sinai School of Medicine in New York, for his pioneering work on the pathogenesis of hepatic fibrosis, which ultimately led to the discovery of hepatic stellate cells.