

- and the decline in peptic ulcer disease—a hypothesis. *Gut* 1986; **27**: 239–42.
- 2 Gibney MJ. Dietary essential fatty acids and peptic ulcer disease. *Gut* 1986; **27**: 1107–8.
 - 3 Hollander D, Tarnawski A. Dietary essential fatty acids and peptic ulcer disease. *Gut* 1986; **27**: 1108–9.
 - 4 Brenner RR. Nutritional and hormonal factors influencing desaturation of essential fatty acids. *Progr Lipid Res* 1981; **20**: 41–7.
 - 5 Robert A, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl and thermal injury. *Gastroenterology* 1979; **77**: 433–43.
 - 6 Tarnawski A, Hollander D, Stachura J, *et al*. Is linoleic acid (dietary essential fatty acid) cytoprotective for the gastric mucosa? [Abstract]. *Gastroenterology* 1985; **88**: 1610.
 - 7 Miller T. Protective effects of prostaglandins against gastric mucosal damage: Current knowledge and proposed mechanisms. *Am J Physiol* 1983; **245**: G601–23.
 - 8 Hawkey CJ, Walt RP. Prostaglandins for peptic ulcer: A promise unfulfilled. *Lancet* 1986; *ii*: 1084–7.
 - 9 Nervi AM, Peluffo RO, Brenner RR, Leikin AI. Effect of ethanol administration on fatty acid desaturases. *Lipids* 1980; **15**: 263–8.
 - 10 Horrobin DF. A biochemical basis for alcoholism and alcohol-induced damage inducing the fetal alcohol syndrome and cirrhosis: Interference with essential fatty acid and prostaglandin metabolism. *Med Hypotheses* 1980; **6**: 929–42.
 - 11 Huang YS, Das UN, Horrobin DF. Effect of dexamethasone on the distribution of essential fatty acids in plasma and liver phospholipids. *IRCS Med Sci* 1986; **14**: 180–1.
 - 12 Hollander D, Tarnawski A, Ivey KJ, *et al*. Arachidonic acid protection of rat gastric mucosa against ethanol injury. *J Lab Clin Med* 1982; **100**: 296–308.
 - 13 Tarnawski A, Hollander D, Stachura J, Krause WJ. Arachidonic acid protection of gastric mucosa against alcohol injury: Sequential analysis of morphologic and functional changes. *J Lab Clin Med* 1983; **102**: 340–51.
 - 14 Baner RF, Bianchi RG, Casser J, Goldstin B. Comparative mucosal protective properties of misoprostol, cimetidine and sucralfate. *Dig Dis Sci* 1986; **31**: 815–55.
 - 15 Diel F. Effects of somatostatin and gamma-linolenic acid (Efamol) on the ethanol hemorrhagic gastric erosion in the rat [Abstract]. *Dig Dis Sci* 1985; **30**: A-9.
 - 16 Boyd EJS, Wormsley KG. Etiology and pathogenesis of peptic ulcer. In: *Bockus gastroenterology* Vol 2. New York: W B Saunders. 1985; 1013–59.
 - 17 Terano T, Salmon JA, Higgs GA, Moncada S. Eicosapentaenoic acid as a modulator of inflammation. Effect on prostaglandin and leukotriene synthesis. *Biochem Pharmacol* 1986; **35**: 779–85.
 - 18 Begin ME, Eells G, Das UN, Horrobin DF. Differential killing of human carcinoma cells supplemented with n-3 and n-6 polyunsaturated fatty acids. *J Natl Cancer Inst* 1986; **77**: 1053–62.
 - 19 Begin ME, Das UN, Eells G, Horrobin DF. Selective killing of human cancer cells by polyunsaturated fatty acids. *Prostaglandins Leukotrienes Med* 1985; **19**: 177–86.

Reply

SIR,—We thank Dr Das and colleagues for their letter concerning our publication (Dietary essential fatty acids and the decline in peptic ulcers disease – a hypothesis, *Gut* 1986; **27**: 239–42). Our main thesis is that the marked decline in peptic ulcer incidence and virulence could be because of the concomitant increase of more than 200% in the ingestion of linoleic acid by the population in the USA and Great Britain. The reasons we proposed this hypothesis are that we have demonstrated that linoleic¹ or arachidonic^{2,3} acid administration to animals can protect against mucosal injury. Moreover, it is well established that the gastroduodenal mucosa can convert these dietary essential fatty acids into prostaglandins of the E-1 or E-2 variety.⁴

Dr Das and colleagues propose that essential fatty acids themselves could perhaps be protective without conversion to prostaglandins. We disagree.

To support their contention, Dr Das *et al* report the use of evening primrose oil in six patients with duodenal ulceration, who 'healed completely' after four to six weeks of therapy. Evening primrose oil contains 70% linoleic acid and 9% gamma-linolenic acid (GLA). Both substances are rapidly converted by the gastroduodenal mucosa to prostaglandins. Thus, all that can be reasonably concluded from this information is that the oral administration of prostaglandin precursor fatty acids was associated with healing of duodenal ulceration. There is nothing in this information that would suggest that the fatty acids have a direct cytoprotective or healing property *not* due to their conversion to prostaglandins. We are not aware of any information that would suggest that dietary essential fatty acids have a prostaglandin independent cytoprotective action. In fact, in our own experiments, we have been able to abolish much of the protective effect of arachidonic acid by pretreating the animals with the cyclooxygenase inhibitor-indomethacin.⁵

We must disagree with another point made by Das and colleagues. They stated that they 'believe that probably gamma linolenic acid is more active than linoleic acid in augmenting peptic ulcer healing.' We are not aware of any experimental evidence that shows this claim. Our own studies of alcohol injury in the rat showed that on a molar basis, arachidonic acid is more potent in preventing alcohol injury than linoleic acid.⁴ We have not however, examined gamma linolenic acid as a cytoprotective agent nor has any one else to our knowledge.

We thank Dr Das *et al* for their comments which call attention to the biological and therapeutic implications of our hypothesis.

DANIEL HOLLANDER AND ANDRZEJ S TARNAWSKI

California College of Medicine,
University of California,
Irvine, Ca. 92717, USA.

References

- 1 Tarnawski A, Hollander D, Gergely H. Protection of the gastric Mucosa by linoleic acid – a nutrient essential fatty acid. *Clin Invest Med* 1987; (In press).
- 2 Hollander D, Tarnawski A, Ivey KJ *et al.* Arachidonic acid protection of rat gastric mucosa against ethanol injury. *J Lab Clin Med* 1982; **100**: 286–308.
- 3 Tarnawski A, Hollander D, Stachura J *et al.* Arachidonic acid protection of gastric mucosa against alcohol injury: sequential analysis of morphologic and functional changes. *J Lab Clin Med* 1983; **102**: 34–51.
- 4 Tarnawski A, Hollander D, Stachura J, Krause WJ, Zipser RD, Gergely H. Cytoprotection of the gastric mucosa by essential fatty acids (EFA) – Prostaglandins precursors. [Abstract]. *Dig Dis Sci* 1985; **30**: 404.

The need for confidence intervals in reporting clinical trials

SIR,—At first glance Lucey *et al's* randomised controlled trial of bran in irritable bowel syndrome (*Gut* 1987; **28**: 221–5) appears to show that this treatment amounts to no more than trial by bran. Before accepting their conclusion that the beneficial effects of bran are due to a placebo response, however, it is instructive to calculate the confidence interval on which they base this conclusion.

According to Figure 1 of their paper, 10 (70%) of 14 patients had a reduction in symptom score of greater than 2 after three months on bran biscuits, compared with 8 (57%) of 14 patients on placebo biscuits for three months. Using conventional methods for calculating the standard error of the difference between two sample proportions, the 95% confidence interval around the 14% difference in response, runs from –20% to +50%.^{1,2} In other words, the trial result is compatible with the true proportion of subjects responding to bran being 50% more than the proportion responding to placebo. This is a difference I think most clinicians would regard as worth obtaining. Indeed, considering the lack of efficacy of drugs and other measures in irritable bowel syndrome, a difference of only 20% might be regarded as worth obtaining.

Similar considerations apply to Chapman *et al's* trial of metronidazole in acute ulcerative colitis (*Gut* 1986; **27**: 1210–2). In that study 14 (74%) of 19 patients receiving metronidazole recovered without colectomy compared with 14 (70%) of 20 patients not receiving metronidazole. The 95% confidence interval on this difference extends from –24% to +32%. Again, this interval includes a potential benefit many clinicians might regard as worth having, as well as the potential for harm.

The authors of both these papers may well be right about their conclusions, but equally, these two small trials are open to considerable risk of Type 2 errors – that is, they may falsely accept the null hypothesis of there being no difference when important clinical differences do exist.³ Some may argue as to whether a 50% benefit from taking bran or a 32% benefit from metronidazole are clinically important but at least by stating a confidence interval, referees and readers can judge for themselves. Surely *Gut* should now adopt the policy of other leading journals and ask authors to state the relevant confidence intervals?

RICHARD F A LOGAN

Department of Therapeutics,
Floor C, South Block,
University Hospital,
Nottingham NG7 2UH

References

- 1 Bulpitt CJ. Confidence intervals. *Lancet* 1987; *i*: 494–7.
- 2 Gardner MJ, Altman DG. Confidence intervals rather than P values: estimation rather than hypothesis testing. *Br Med J* 1986; **292**: 746–50.
- 3 Freiman JA, Chalmers TC, Smith H, Kuebler RR. The importance of beta, Type II error and sample size in the design and interpretation of the randomised control trial. *N Engl J Med* 1978; **299**: 690–4.

Reply

SIR,—Thank you for the opportunity to respond to Dr Logan's letter. In our study of the efficacy of bran in irritable bowel syndrome, on comparing the initial response to bran or to placebo in two groups of 14 subjects; or on comparing in a crossover fashion the responses to bran and placebo in all 28 subjects; or finally on stratifying the subjects according to the effect of bran on stool weight, no therapeutic advantage of bran over placebo could be demonstrated.¹ Thus we could not reject the null hypothesis that bran and placebo are similar. The possibility of a Type 2 error exists in any study which does not reject the null hypothesis. In studies such as ours, however, given the relatively small numbers, a confidence interval based on either data from the initial treatment period or the crossover analysis is likely to contain zero, be fairly wide and include both positive and negative values. Therefore this is not an appropriate setting for this form of analysis as the result always will be too diffuse to be meaningful. Confidence intervals are of value in larger studies in which the null hypothesis is rejected because they allow the reader to judge whether a statistical significant observation is of clinical significance.²

MICHAEL R LUCEY

Department of Internal Medicine,
Division of Gastroenterology,
University of Michigan Medical Center,