tional' period, a non-enteric-coated preparation should be substituted in the 'cimetidine' period as enteric coating delays tablet dissolution even at pH 6. Finally, and most importantly, the diet should be changed between the two periods to take full advantage of cimetidine's effect. An improvement in fat excretion from, say, 50 g/d to 10 g/d would give the patient an extra 360 Kcal/d from fat and correspondingly less from protein and perhaps carbohydrate. This is insufficient to improve nutritional status markedly. What cimetidine does is to decrease the slope of the regression of fat excretion on fat intake, as shown by the Toronto group.² Patients whose intake is, as it usually is, limited by symptomatic steatorrhoea should therefore be able to eat as well as absorb more with adjunctive cimetidine treatment. Only by maximising fat intake separately during the 'conventional' and 'cimetidine' periods can the full nutritional effect of the drug be assessed. In effect, the trial is of a therapeutic strategy based on cimetidine, rather than of the pharmacological effect of the drug.

In our experience the effect of cimetidine, in carefully selected patients, is usually obvious both in terms of fat absorption and nutritional status. If it is not, or if airways resistance increases on routine monitoring, the drug should be stopped. Whether improving nutrition by this means improves pulmonary function is a more worthy, but as yet unanswered, problem for investigation in a controlled trial.

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Dietary essential fatty acids and peptic ulcer disease
SIR,—In a recent leading article (*Gut* 1986; **27**: 239-42) Hollander and Tarnawski presented data to support their hypothesis that the decline in peptic ulcer disease over the past few decades is associated with the increased intake of the dietary essential fatty acid, linoleic acid, during the same period.

Their evidence was both epidemiological and metabolic and may be criticised on both grounds.

The authors provide experimental evidence that the intragastric administration of either linoleic or arachidonic acid reduces the severity of rat gastric ulceration. Both acids were presented in the free form together with an appropriate solubilizer. Free fatty acids or their salts (soaps) are not consumed by man whose dietary fat is entirely esterified mainly as triglyceride and with small amounts of phospholipid. Proximal to the pancreatic duct (where the great majority of peptic ulcers occur), dietary fat remains esterified and in the non-aqueous phase. As such it is not available for exchange with intestinal cells. Furthermore, arachidonic acid is consumed by man in extremely small amounts because arachidonic is neither a component of vegetable fats, nor is it a component of the triglycerides of animal fats. Together these account for over 99% of our dietary fat. The small amount of dietary arachidonic acid consumed by man (ca 25 mg/d or 0.03% fatty acids) is derived from meat and milk phospholipids. Even this remains esterified proximal to the availability of pancreatic lipase. It is thus difficult to see how free linoleic acid or arachidonic acid could be made available in the human gut in that region where ulceration normally occurs and hence a local effect is difficult to envisage.

To hypothesise that increased local cytoprotection of the intestinal mucosa may arise from an increased metabolic pool of arachidonic acid, through intakes of dietary linoleic acid is also difficult to accept. Arachidonic acid is found almost exclusively in the phospholipid fraction of serum lipoproteins and cell membranes where it contributes about 25% of the fatty acids in the Sn-2 position. The turnover of this pool is extremely slow in unstimulated cells and consequently a prolonged period of essential fatty acid deficiency is required to reduce the phospholipid levels of arachidonic acid. Such a deficiency state occurs in man only under extreme circumstances such as the misuse of parenteral nutrition. On the other hand, raising the intake of dietary linoleic acid does not increase the cellular pool of arachidonic acid as that is determined by the mass of phospholipid (and hence membrane) per cell. There is no evidence from animal studies to suggest that dietary corn oil, rich in linoleic acid, increases cell or serum phospholipid arachidonic acid above that achieved when the nutritional requirements for essential fatty acids are met.

The authors propose that the factor linking the fall in the incidence of peptic ulcer disease and the rising intake of essential fatty acids is prostaglandin E₂ (PGE₂). The eicosanoids are undoubtedly linked to peptic ulcer disease but, surely, any factor

which provided additional substrate for PGE₂ synthesis would also provide additional substrate for the synthesis of prostacyclin, thromboxane, and the leukotrienes. The authors provide no indication as to the effect of increased linoleate intake on the balance of eicosanoids, or of the effects of changes in this balance on the course of peptic ulcer disease.

The proposed hypothesis relies heavily on the epidemiological evidence linking the decline in peptic ulcer disease with the rise in essential fatty acid intake. Their data shows that between 1909/1913 and 1980, there has been a 300% increase in the intake of linoleic acid while during the same period the intake of saturated fatty acids has increased by only 10%. Does this mean that the rise in the incidence of coronary heart disease is not after all associated with a rise in the intake of saturated fats but with a rise in the intake of the polyunsaturated essential fatty acids? This dubious epidemiological evidence must be supported by other data for tentative acceptance of this hypothesis. One would need to know whether what is reportedly seen for the USA as a whole, is also evident with different age-groups, different regions of the USA, for men and women, etc. Equally one would require international comparisons of diet and peptic ulcer disease.

Science proceeds through the integrated processes of conjecture and refutation. In proposing a hypothesis, vagueness should be avoided and precision encouraged. Just as there are rules in refutation there are rules in conjecture, otherwise we may just as well take up astrology.

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Reply

SIR,—We appreciate the opportunity to respond to Dr Gibney's letter. Dr Gibney questions the concept that long term increase in dietary linoleic acid ingestion could influence cell membrane content of prostaglandin precursors and the generation of prostaglandins.

When linoleic acid is ingested (as a triglyceride) it is absorbed in the jejunum and converted to dihomogamma-linolenic acid and arachidonic acid which are then stored as membrane phospholipids in many organs including the stomach and duodenum. When the tissues are stimulated, phospholipases are activated, mobilising the fatty acids and initiating their conversion to prostaglandins.

The literature is replete with reports showing that supplemental feeding of linoleic acid to man or animals does indeed result in increased membrane prostaglandin precursors.¹⁻⁸ A recent report of chronic high linoleic acid feeding in the rat showed enhanced endogenous PGE₂ production, decreased basal acid secretion, and protection against stress ulcerations.⁹ Thus, Dr Gibney's points expressed throughout the first three paragraphs of his letter are unsubstantiated by published scientific reports and runs counter to published research data.¹⁻⁹

Dr. Gibney's fourth paragraph raises a point which is important but is not clearly understood. The feeding of linoleic or arachidonic acids on a chronic basis results in storage of the fatty acids in cell membrane phospholipids. The specific type of cells in the tissues—for example, macrophages—can determine the type of prostanoid formed. Thus, linoleic acid feeding does not necessarily result in elaboration of thromboxanes in the gastroduodenal mucosa. Instead, in our experiments we find that arachidonic acid administration induces predominantly the synthesis of PGE₂¹⁰ while linoleic acid administration results predominantly in the synthesis and release of PGE₁.¹¹

In his fifth paragraph, Dr Gibney tries to fault our hypothesis because it does not explain 'the rise in the incidence of coronary heart disease'. The thrust of this argument is impertinent to our hypothesis. Our paper is about ulcer disease, not coronary heart disease. Furthermore, published scientific data show that the incidence of coronary disease has been decreasing in the USA and that the feeding of linoleic acid lowers serum cholesterol decreases platelet thrombosis, and decreases cardiovascular mortality in human trials.^{12 13}

The strength of our hypothesis¹⁴ rests on three separate factors. Well established epidemiological data, enumerated in our publication, clearly show that the incidence and the virulence of peptic ulcer disease have decreased over the past few decades. Concomitantly, the dietary ingestion of linoleic acid by the general population has increased dramatically. Because our published experiments have clearly shown that linoleic and arachidonic acids can be converted to prostaglandins which can protect the gastroduodenal mucosa against injury,^{10 11} we proposed that the increase in dietary intake of linoleic acid could account for the decreasing incidence and virulence of peptic disease. Thus, our hypothesis rests on firm biochemical, experimental, and epidemiological finding and is amply supported by well established reports in the literature. Dr Gibney accused us of having an astrological leaning. Our careful reading of his letter leads us to wonder