costs are measured in monetary terms. Our analysis is structured in a manner that facilitates a direct comparison of the costs per patient relieved of symptoms. Such a structure enables outcome variations to be directly incorporated into the analysis as and when such evidence is generated. Information about cost is useful only when considered jointly with information about clinical outcomes and further research concerning the long term cost and outcome of treatment is currently in progress.

The Nijmegen group's reference to "effect modification" and its potential effect of diluting variations between the therapeutic options is irrelevant in the context of our paper. The aim of good prescribing is to segment general patient populations to ensure that the therapeutic requirements of individual patients are optimally met by the prescriber. Obviously, in their day to day workload primary care physicians also frequently encounter patients with recurrent GORD as well as with H_2 refractory and complicated GORD. Cost effectiveness calculations on "undefined" GORD would inevitably favour omeprazole given that it causes the greatest suppression of acid secretion in patients with severe disease. We make no claims concerning the applicability of the analysis to undefined GORD but simply assert that the extent of acid suppression generated by omeprazole may not be necessary for first episodes of uncomplicated GORD. If this is the case, then hard pressed clinicians will be able to conserve their scarce health care resources for investment elsewhere.

Dr Crawley questions the numerical basis for the analysis. Our sample was generated as a random selection from the entire eligible MediPlus database for 1995 using the software random number based sample selection function. The sample chosen was selected on the basis of manageability given that an individual review of each patient record was required. The reduction from 279 to 257 patients was simply to increase the level of patient homogeneity as outlined in the original paper. Both Crawley and Bate also refer to a large body of evidence supporting the clinical and economic superiority of omeprazole. Unfortunately, for our purposes the vast majority of such evidence is irrelevant given that it does not specifically analyse prescribing in practice for new patients presenting at the primary care level with mild to moderate GORD. Dr Crawley's belief in the superiority of omeprazole due to the lack of need for dose titration is puzzling. The British National Formulary's recommendation for GORD is for 20 mg daily for four weeks, followed by 40 mg for four to eight weeks as required, reduced to 10 mg for long term management, increased to 20 mg if symptoms recur. Dr Crawley's further belief that patients may respond to treatment failure by simply doing nothing also is difficult to substantiate. It is reasonable to assume that individual patients exhibit a personal threshold of tolerance to the symptoms of GORD above which they seek professional advice. Such a threshold will vary significantly between patients but is likely to be fairly stable within the same patient. In such circumstances it is difficult to see why a patient would not seek further professional advice in cases where the initial prescription did not reduce symptomatology below their personal threshold.

Many of the issues raised reflect the fact that many gastroenterologists only come into

Table 1 Risk of admission to hospital with drug induced liver injury in those taking NSAIDs plus one other drug known to cause sporadic liver injury

NSAID	Hepatotoxin	Controls	Cases	Odds ratio	95% CI
—	—	294	7	Reference	
+	—	99	5	2.1	0.6 to 7.0
—	+	67	11	6.9	2.5 to 19.4
+	+	40	11	11.6	4.2 to 32.9

CI, confidence interval.

contact with the tip of the iceberg with regard to GORD. By supporting 95% of patients without recourse to specialist advice, primary care physicians ensure gastroenterologists encounter a very thin slice of reality with regard to the optimal treatment of GORD. The vast majority of treatments are initiated without prior investigation and where empiricism is successful such patients do not come to the attention of gastroenterologists. Although this may be appreciated intellectually by gastroenterologists, our paper provides powerful re-enforcement of the nature of the division of labour between primary care physicians and gastroenterologists in the treatment of reflux disease.

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Diagnostic value of T cell reactivity in drug induced hepatitis

EDITOR,—I read with interest Maria and Victorino's work (*Gut* 1997;41:534–40) on the diagnostic value of specific T cell reactivity to drugs in 95 cases of drug induced liver injury. They are to be congratulated on assembling the largest group of patients with suspected drug induced hepatotoxicity and attempting to assess causality using their lymphocyte test.

In their discussion, when referring to the clinical significance of the presence of prostaglandin producing suppressor cells in vitro, they state that, "patients in which this phenomenon was detected had a less severe disease, as assessed by aminotransferase concentrations and more rapid cure." There is another potential clinical significance to the interpretation of their in vitro results and that is that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity in this unpredictable, hypersensitivity type of liver injury. Gutthann and Rodriguez¹ showed that patients taking an NSAID plus one other drug known to cause sporadic liver injury were at almost twice the risk of being admitted to hospital with biochemical and clinical evidence of liver disease than those taking a potentially hepatotoxic drug alone (table 1).

It would be interesting to know in Maria and Victorino's group of patients how many were taking an NSAID in addition to the suspected hepatotoxin and whether this was

higher than in their control groups or a standard adult population.

Given the large number of patients that consume NSAIDs, even a small increase in the risk of potentiating hypersensitivity reactions to other drugs, including organs other than the liver, could represent a major health issue.

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- 1 Gutthann SP, Rodriguez LAG. The increased risk of hospitalisations for acute liver injury in a population with exposure to multiple drugs. *Epidemiology* 1993;4:496–501.

Reply

EDITOR,—We showed that the in vitro phenomenon of putative prostaglandin producing suppressor cells demonstrated in patients with drug induced hepatitis was significantly associated with a less severe form of disease and a more rapid cure. It is possible to speculate that this in vitro phenomenon could also occur in vivo and play a part in the down regulation of the immune response triggered by the drug or its metabolites.

We think that Dr Bartle's point suggesting that there is another potential clinical significance to the interpretation of our in vitro results, namely that non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of developing drug induced hepatotoxicity, is a very interesting possibility. Our own epidemiological data are consistent with the results of the epidemiological study presented by him, showing that patients taking NSAIDs have an increased risk of developing liver injury induced by other drugs. In fact, we compared the frequency of NSAID consumption in our population with drug induced liver injury with two different adult populations integrated into prospective studies, one consisting of patients admitted to our internal medicine unit in the University Hospital and the other consisting of patients followed in the primary care setting (table 1). Patients with drug induced hepatitis took significantly more NSAIDs than the control populations (χ^2 test, $p < 0.0001$).

Although all epidemiological evidence suggests that NSAIDs increase the risk of hepatotoxicity from other drugs, the possibility that this could have an immunological basis

Table 1 Consumption of NSAIDs by patients with drug induced hepatitis and two control populations

	Patients with drug induced hepatitis	Patients admitted to hospital	Population of a health centre
Number of cases	136	277	1723
Mean age	46.7	63.9	44.6
Number taking NSAIDs	43	40*	206
Percentage	32	14	12

* Took NSAID in the 15 days prior to admission.

has to be viewed with caution. In fact, it has been shown that prostaglandin E₂ has a protective effect in cases of hepatitis induced by hepatotoxic agents and cytopathic viruses, both in animal models and in humans,¹⁻³ suggesting that a non-immunological mechanism may also be involved in this association.

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Guidance for trials in *Helicobacter pylori* infection

EDITOR.—Your prestigious journal has recently published a supplement on guidelines for clinical trials in *Helicobacter pylori* infection (*Gut* 1997;41(suppl 2):S1-23). I welcome these guidelines, and as it would be expected from the authors' experience and background, the term excellent would surely be adequate to describe the three different papers contained in the supplement. There are, however, at least two key points that merit discussion before these guidelines are generally applied by the scientific community.

Firstly, a methodological point. Double blind, randomised, controlled, well planned and developed trials do provide very sound and solid scientific evidence for evaluating efficacy. However, other types of trials, even uncontrolled, can give very valuable data on effectivity, and cannot be discarded as long as methods and analysis are correct. In fact, some of the most cited articles are uncontrolled but very elegant studies^{1,2} and some are even case reports.³ Sometimes classic methodological rules are avoided but good science is produced.⁴

Secondly, an ethical point. In the guidelines (pS3) the following sentence is included, "In phase III studies, aiming at regulatory approval of a new drug regimen, one of the reference groups should be given a treatment known to result in no eradication of *H pylori*...". This assertion is clearly in conflict with the Declaration of Helsinki, mentioned as an ethical reference by the authors on the same page. As recently pointed by Angell,⁵ the Declaration of Helsinki states, "In any medical study, every patient—including those of a control group, if any—should be assured of the best proven diagnostic and therapeutic method". If prospective study subjects have peptic ulcer disease, current recommendations are mandatory: *H pylori* should be eradicated.⁶ In fact, the same group of authors have very recently stated in *Gut* that, "...*H pylori* eradication is strongly recommended in all infected patients with a diagnosis of duodenal or gastric ulcer disease, past or present...", a sentence based on "unequivocal supporting evidence".⁷ I think that patients should come first and methodology second,^{8,9} and strongly suggest that this sentence should be removed from the guidelines, or at least

limited to pathologies with "equivocal" evidence such as functional dyspepsia.

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- 8 Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the Human Immunodeficiency Virus in developing countries. *N Engl J Med* 1997;337:853-6.
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Clinical trials in *Helicobacter pylori* infection

EDITOR.—We read with great interest the excellent guidelines for clinical trials in *Helicobacter pylori* infection published last September (*Gut* 1997;41(suppl 2):S1-23). The recommendations almost without exception, are extremely useful. We feel, however, that one or to points might be expanded, or deserve extra comment.

As the working party states, most of the studies published on eradication therapy are non-comparative or are not large enough to reach a definite conclusion. This is because the sample size required to rule out a 10% difference between treatment groups for a two-branch comparative study is nearly 600 patients.¹ To our knowledge no studies of this size have been published to date and, therefore, the length and composition of ideal eradication therapy has to be determined in large multicentre trials.

Inclusion criteria, initial evaluation, and follow up in these large eradication studies should be as simple as possible in order to allow inclusion of such a large number of subjects with minimal disturbances for both investigators and patients.

In more than one place, the guidelines call for two positive diagnostic tests for a patient to be considered reliably infected by *H pylori* and included in a treatment study. However, the reliability of diagnostic tests largely depends on the prevalence of *H pylori* infection in the population studied. When studying a population known to harbour a very high prevalence of infection, such as patients with duodenal ulcer, two diagnostic tests are not necessary. A simple statistic calculation applying the Bayes theorem will show that in these patients a single diagnostic test—even serology—will be enough to confirm the diagnosis of *H pylori* infection. In brief, if we assume that the prevalence of infection is at least 90-95% in patients with duodenal ulcer, even assuming an exceptionally low sensitivity and specificity of 80% for the diagnostic technique, the predictive value of a positive result ranges between 97

Figure 1 Predictive value of a positive serological test for *H pylori* in patients with duodenal ulcer. Positive predictive value = $72/(72+2) \times 100 = 97.2\%$. Patients with duodenal ulcer are assumed to have a 90% prevalence of *H pylori* infection. Data have been calculated for a sensitivity and specificity of 80% for the serological test.

Figure 2 Value of a negative UBT to evaluate cure of *H pylori* infection after treatment. Negative predictive value = $72/(72+2) \times 100 = 97.2\%$. The eradication rate is assumed to be 80%. Data have been calculated for sensitivity and specificity of 90% for the UBT.

and 99%. This is shown graphically in fig 1. Using more sensitive and specific tests such as histology or the urea breath test (UBT), the predictive value of a positive result will rise to almost 100%. Therefore, a second test will only add cost to the study, and will lead to the exclusion of a valuable percentage of patients with false negative results in the second test.

Similar reasoning can be applied to the post-treatment controls. If we compare treatments with an effectivity of over 80% and perform a six week UBT (assuming a sensitivity and specificity of 90% for the technique)³ the predictive value of a negative test result is over 97% (fig 2). This predictive value increases when the efficacy of the treatment and the specificity of the test increase. Therefore, a second test is probably unnecessary. We agree that patients with a positive UBT after treatment should undergo endoscopy, but for different reasons: the predictive value of a positive UBT after treatment is low, and nearly one third of patients will be cured despite a positive post-treatment UBT (fig 2).

Finally, the time for control is not clearly defined. Four weeks may be too short a period for control. Studies of eradication follow up have shown a 5% "recrudescence" rate after apparently effective treatment. However, these late failures are rare beyond 4-6 months after treatment.³ Therefore, the longer the period between the treatment and the UBT the more reliable the results will be. The possibility of performing a single test after 3-4 months should therefore be considered.

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