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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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)² 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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