Letters

The WHO wants governments to encourage people to stop smoking

We have received the following open letter from the regional director for Europe of the World Health Organisation. It is addressed to the heads of government of the 51 European member states of the WHO.

Dear Prime Minister,

All the really difficult problems in your country's development land on your desk. From morning to night your schedule overflows with burning issues that claim your attention. Setting priorities is a constant challenge. There are times, however, when a small effort on your part can make a large contribution to the quality of life of the people of your country. This is one of those times, because you alone can orchestrate the concerted action of many ministries. I am addressing you today on such a matter, to ask for your support. Help your people by reducing the awful threats to their life and health that smoking inflicts on them.

Tobacco is one of the greatest public health challenges facing the 51 member states of the WHO European region. Every year over 1.2 million deaths in the region are caused by tobacco. By 2020, unless we really change things, that number will rise to two million deaths. This will represent a fifth of all deaths, the single greatest killer in the European region. Many of these deaths occur among the economically active segment of the population.

The facts are simple. Manufactured tobacco products deliver regulated doses of the addictive drug nicotine. Tobacco products cause one third of all cancers and a large proportion of heart disease, as well as many other health problems, and half of all regular smokers die of a condition caused by smoking. Over one third of adults in the region are regular daily smokers, and smoking is increasing in two fifths of the countries in the region, particularly among young people and women. Although there are some notable exceptions, why are we failing so miserably to deal with this problem when we so clearly know what to do?

Almost every minister of health in our member states now sees this as a major challenge to health—both for this and for future generations—and many have taken vigorous action to deal with the issue. I am also proud to report that we have strong support from virtually every national medical association, national pharmaceutical association, and pharmacy-owner association in the region, for an all out effort to help young people to stop smoking and actively support those smokers who want to "kick the habit."

Such action cannot, however, be carried out by ministries of health alone; they need support and active cooperation from a number of other ministries—and for that they need your personal commitment. As the leader of the country, you have the power, if your country has not already done so:

- To appoint an intersectoral coordinating committee for tobacco control, responsible for drawing up effective and comprehensive action plans on tobacco, with clear timetables for implementation and specific targets for reductions in the use of tobacco, and adequately funded commensurate with the burden of disease caused by tobacco, possibly from tobacco tax or a special levy on tobacco products
- To persuade colleagues in the ministries of finance that regular increases in tobacco tax can raise revenue, correct for externalities such as health costs, and deter tobacco consumption;
- To persuade colleagues in government that there is a causal relation between advertising and smoking behaviour, particularly in young people, and that effective action requires a total ban on tobacco advertising and the prohibition of sponsorship associated with a tobacco brand name or product
- To persuade colleagues in government that restricting the access of people younger than 18 to tobacco products is effective in reducing the number of adolescents and young adults who become daily smokers
- To ensure that all health related premises and particularly those within the jurisdiction of the ministries of health are smoke free environments
- To ensure that support for smoking cessation is made widely available, particularly through primary healthcare professionals, including doctors, nurses, pharmacists, and dentists
- To persuade colleagues in the ministries of customs and excise that failure to control tobacco smuggling is costing the country revenue and lives.

It is time to take a stand and say things that may not be popular. During the next decade over 12 million men and women will die an agonising death from diseases caused by smoking, leaving in their wake countless family tragedies and great economic loss to our societies. Unless we take strong action now, future generations will condemn us for failure to control one of the worst scourges facing our people today.

Yours sincerely,

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Advice to authors

We receive more letters than we can publish: we can currently accept only about one third. We prefer short letters that relate to articles published within the past four weeks. We also publish some "out of the blue" letters, which usually relate to matters of public policy.

When deciding which letters to publish we favour originality, assertions supported by data or by citation, and a clear prose style. Letters should have fewer than 400 words (please give a word count) and no more than five references (including one to the BMJ article to which they relate); references should be in the Vancouver style. We welcome pictures.

Letters should be typed and signed by each author, and each author's current appointment and address should be stated. We encourage you to declare any conflict of interest. Please enclose a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected.

We may post some letters submitted to us on the world wide web before we decide on publication in the paper version. We will assume that correspondents consent to this unless they specifically say no.

Letters will be edited and may be shortened.

Validation of a rapid whole blood test for diagnosing *Helicobacter pylori* infection

Conflicting results from the Helisal test

EDITOR—P Moayyedi and colleagues are not correct in stating that the accuracy of the Helisal test for diagnosing *Helicobacter pylori* had not been independently evaluated before their report.[1] As shown in the table, several groups have now reported their findings. The results show a variation in the accuracy of the test that was not revealed by Moayyedi and colleagues' results.

Why are their results rather better than those of others? They do not mention any problems in interpreting the tests, although two groups found 5-10% of tests difficult to read (Stone et al; Lahaie et al (table)); we also

Table 1 Accuracy of Helisal test for diagnosing *H pylori* infection in six studies

Reference	Year	No of patients	Sensitivity (95% CI) (%)	Specificity (95% CI) (%)	Prevalence of *H pylori* positivity (%)
Yapp et al (*Gut* 1995;37(suppl 1):A224)	1995	69	93 (73 to 97)	88 (78 to 99)	47
Stone et al (*Gut* 1996;39(suppl 2):A110)	1996	100	95 (NA)	55 (NA)	46
Peitz et al (*Gastroenterology* 1996;110(suppl 4):A226)	1996	147	78 (71 to 85)	81 (75 to 87)	68
Duggan et al[2]	1995, 1996	173	81 (74 to 89)	73 (61 to 84)	62
Crane et al (*Gut* 1996;39(suppl 2):A121)	1996	219	96 (NA)	55 (NA)	33
Lahaie et al (*Gastroenterology* 1996;10(4):A167)	1996	256	89 (NA)	89 (NA)	NA
Moayyedi et al[1]	1997	175	88 (79 to 94)	91 (82 to 97)	55

NA=not available.

found a similar difficulty. In one study there was disagreement between two observers in 6% of cases (Stone et al (table)). Another important point omitted by Moayyedi and colleagues was the type of blinding used to ensure that the tests were read independently. Were the Helisal tests read before or after the endoscopy?

We are puzzled as to why the authors emphasise the number of endoscopies avoided using a test intended primarily for use in primary care. Whereas screening for *H pylori* in patients already referred to hospital may prove cost effective, the existing evidence suggests that screening for *H pylori* in primary care and then referring positive cases for endoscopy is not a cost effective strategy.[3] It would be even less so if the Helisal test performs as poorly as others have found.

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1 Moayyeddi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997;314:119. (11 January.)
2 Duggan A, Logan RPH, Knifton A, Logan RFA. Accuracy of near-patient blood tests for Helicobacter pylori. *Lancet* 1996;348:617.
3 Briggs AH, Sculpher MJ, Logan RPH, Aldous J, Ramsay ME, Baron JH. Cost effectiveness of screening for and eradication of Helicobacter pylori in management of dyspeptic patients under 45 years of age. *BMJ* 1996;312: 1321-5.

Assessment lacked certain considerations

EDITOR—In presenting the results of their validation of the Helisal rapid blood test for diagnosing *Helicobacter pylori* infection, P Moayyedi and colleagues rightly emphasise that the test needs evaluating in the area in which it is to be used.[1] The high sensitivity and specificity found in their study are not generally reproducible. Similar evaluations carried out by us and by others have found much lower specificity.[2 3] In a study of a multiethnic population,[4] we calculated a range for sensitivity and specificity according to whether patients with equivocal *H pylori* status were deemed to be positive or negative. In 171 patients we found an overall sensitivity of 91-92% (95% confidence interval 82% to 97%), with a specificity of 56-62% (45% to 72%). Even in patients under 45 years of age the specificity was poor and the test performed particularly badly in patients of south Asian origin.

Results of the Helisal test are read subjectively by eye. Two definite limitations of the test that were not considered by Moayyedi and colleagues are readability and interobserver error. In our study tests were read by two observers blinded to the other's interpretation. In two (1%) cases the interpretation differed between positive and negative and in a further 20 (10%) the results were considered indeterminate or difficult to read. Overall, 22 (11%) of our results could be considered equivocal.

We agree that the Helisal test may be useful for pre-endoscopy screening of younger patients. However, enthusiasm for this convenient test in reducing endoscopy workload may be premature and should not lead to its widespread use without informed awareness of its limitations.

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1 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter infection. *BMJ* 1997;314:119. (11 January.)
2 Stone MA, Mayberry JF, Wicks ACB, Stevens M, Swann A, Robinson RJ. The Helisal test — an assessment of readability and diagnostic accuracy. *Gut* 1996;39(suppl 2):A110.
3 Crane C, Hay-Kaufman M, Forrest T, Van Kell S. Comparison of three whole blood rapid tests for antibodies to H pylori. *Gut* 1996;39(suppl 2):A121.
4 Stone MA, Mayberry JF, Wicks ACB, Livsey SA, Stevens M, Swann RA, et al. Near patient testing for Helicobacter pylori: a detailed evaluation of the Cortecs Helisal rapid blood test. *Eur J Gastroenterol Hepatol* (in press).

Test needs full evaluation in primary care

EDITOR—Moayeddi and colleagues report an evaluation of the Helisal rapid blood test for diagnosing *Helicobacter pylori* infection in secondary care.[1] However, near patient tests for *H pylori* may become widely used in general practice and it is important it should be evaluated in this setting. Guidelines for the performance of diagnostic test evaluations have been produced by the Cochrane Methods Working Group on Screening and Diagnostic Tests.[2] These guidelines are particularly relevant when no single test can be applied as a gold standard, as is the case with *H pylori*, and where direct tests such as histology, culture, and urease tests on biopsy specimens and indirect test such as urea breath tests (using carbon-13 or carbon-14) and serology may produce false results.[3] Moayeddi and colleagues have attempted to overcome the lack of a gold standard by creating a proxy of two or more out of four tests.[1] However, this study is likely to be particularly prone to spectrum bias—that is, differing sensitivity and specificity in populations with a different prevalence of *H pylori*.[4]

Furthermore, although Moayyedi and colleagues comment on the potential of the test to produce savings if used as a screening test for endoscopy in patients under the age of 45 years, these results are based on patients who had already been referred, not on those who may be referred by this policy. The predictive value of the test in different clinical settings may be calculated from Bayes's theorem, using likelihood ratios derived from Moayeddi and colleagues' data (likelihood ratio for a positive test is 10.1 (95% confidence interval 4.9 to 21.8) and for a negative test is 0.13 (0.07 to 0.23) (table).

Table 1 Variation in predictive values on basis of prevalence of disease

Clinical setting	Prevalence (%)	Positive predictive value (%)	Negative predictive value (%)
Patients with known peptic ulcer disease	90	99	46
Dyspeptic patients (<45 years) in endoscopy department	55	92	86
Dyspeptic patients (<45 years) in general practice	30	80	95

The Helisal test may not have the power to satisfactorily exclude infection when the prevalence is high, but its performance as a screen before endoscopy looks promising; this area is the subject of several randomised controlled trials, and a well established trials collaborators group (chaired by BD) aims to carry out a systematic review on completion of the individual trials. Until the Helisal test has been satisfactorily evaluated in primary care, caution should be expressed in its application.[5] Future studies should evaluate the role of iterative bayesian techniques, such as Gibbs sampling, to produce best estimates in the face of uncertain data. A systematic review of near patient tests in primary care has recently been completed by our department, with recommendations for the conduct of near patient tests evaluations in the primary care setting. This review will be published shortly.

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1 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997; 314:119. (11 January.)
2 Cochrane Methods Working Group on Screening and Diagnostic Tests. Recommended methods, updated 6 June 1996. Available at http://wwwsom.flinders.edu.au/cochrane/
3 Pronovost AD, Rose SL, Pawlak JW, Robin H, Schneider R. Evaluation of a new immunodiagnostic assay for Helicobacter pylori antibody detection—correlation with histopathological and microbiological results. *J Clin Microbiol* 1994;32:46-50.

4 Lachs MS, Nachamkin I, Edelstein PH, Goldman J, Feinstein AR, Scwartz SJ. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Ann Intern Med* 1992;117:135-140.
5 Loy CT, Irwig LM, Katelaris PH, Talley NJ. Do commercial serological kits for Helicobacter pylori infection differ in accuracy? A meta-analysis. *Am J Gastroenterol* 1996;91: 1138-44.

Endoscopy of only those who are positive for *H pylori* could miss other diagnoses

EDITOR—"Reduce endoscopy workload by 66% while detecting all peptic ulcers" could have been a headline resulting from the paper by P Moayyedi and colleagues.[1]

Moayyedi and colleagues reported excellent results for a rapid blood test that detected *Helicobacter pylori* infection (sensitivity 88%, specificity 91%). But the headline applied only to patients who were referred for endoscopy and who were under 45 years of age, as is clearly pointed out by the authors.

However, the authors failed to address the number of patients with diagnoses other than peptic ulcer that might have been missed if only those who had a positive result on testing for *H pylori* underwent endoscopy. Of the 69 patients who had a positive diagnosis at endoscopy, 21 (30%) had oesophagitis and a further 9 (13%) other diagnoses. So 43% of positive endoscopic findings do not relate to the presence or absence of *H pylori*. Perhaps a more appropriate headline could have been: "X% of oesophagitis missed by blood testing for *Helicobacter pylori*."

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1 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997;314:119. (11 January.)

Likelihood ratios should be routinely reported

EDITOR—The paper by Moayyedi and colleagues presented valuable information about the potential for near patient testing using the Helisal rapid blood test for *Helicobacter pylori*.[1] However, the authors did not adopt the recommendations of the Evidence-Based Medicine Working Group on diagnostic tests and calculate likelihood ratios (likelihood ratio = sensitivity/(1 – specificity).[2] The advantage of using likelihood ratios is that it forces clinicians to consider the attributes of the test in relation to the probability of disease in individual patients.

Using the results from Moayyedi and colleagues' paper the value of likelihood ratios can be shown. In that study the likelihood ratio for a positive test result was 9.8. The advantage of knowing this is that it can be applied to similar patients in other populations to estimate the predictive value of the test, provided that the pre-test probability of disease can be estimated. For example, *H pylori* is found in 48% of dyspeptic patients in the community[3] (the pre-test probability), so therefore a positive rapid blood test with a likelihood ratio of 9.8 applied to this population would give a post-test probability (or predictive value) of 90% (this can be estimated using a simple calculation or a nomogram[4]).

The results of this paper could be applied without any further research other than showing that the test can be performed reliably within primary care. The practitioner could be told that a positive rapid blood test in a dyspeptic population would change the probability of the patient being *H pylori* positive from 48% to 90%.

Likelihood ratios provide a useful means for applying research findings to clinical practice. Their reporting should be routine.

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1 Moayyedi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997;314:119. (11 January.)
2 Jaeschke R, Guyatt GH, Sackett DL. Users' guides to the medical literature. III. How to use an article about a diagnostic test. B. What are the results and will they help me in caring for my patients? The Evidence-Based Medicine Working Group. *JAMA* 1994;271:703-7.
3 Bernersen B, Johnsen R, Bostad L, Straume B, Sommer Al, Burhol PG. Is Helicobacter pylori the cause of dyspepsia? *BMJ* 1992;304:1276-9.
4 Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine*. Edinburgh:Churchill Livingstone, 1997.

Likelihood ratios provide more information with little effort

EDITOR—Moayyedi and colleagues soundly validate a rapid whole blood test for diagnosing *Helicobacter pylori* infection, but are their conclusions presented in the most useful way?[1] Take, for example, a hypothetical patient, Joe: a 40 year old man referred to the gastroenterology clinic for investigation of dyspepsia. He is not taking any non-steroidal anti-inflammatory drugs, and the rapid blood test for *H pylori*, performed while he waits in the clinic, gives negative results. What is the chance that he has *H pylori* infection?

Moayyedi and colleagues state that the sensitivity of the test is 88% and the specificity 91%. The positive and negative predictive values are 92% and 86% respectively. Do these values answer the question? Not directly; to do so the likelihood ratios for a positive or negative test result are needed. Likelihood ratios show by how much a given test result will raise or lower the pre-test probability of the target disease. They are easy and intuitive to use[2] and allow knowledge of the accuracy of a test to be combined with local prevalences of disease and individual patient characteristics. When test results form a continuum, such as biochemical concentrations or ultrasound measurements, they also allow the use of multiple cut off points.

Likelihood ratios can be derived from table 1 in Moayyedi and colleagues' paper, but by including them the authors could have offered far more information with little extra effort. In this case, Joe has a 50% chance of having *H pylori* infection before the rapid blood test. (The prevalence of *H pylori* infection in Moayyedi and colleagues' study was 83/154 or 54%.)

With this pre-test probability and a likelihood ratio for a negative test result of 0.13 the answer to the question of whether Joe has *H pylori* infection with a negative result is less than 1%. This result enables him to go home without endoscopy. If the test had been positive (with the likelihood ratio of a positive test of 9.8) his probability of having the infection would be greater than 90%, strongly suggesting the need for endoscopy.

Hopefully in the future authors describing tests will be encouraged to present likelihood ratios.

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1 Moayeddi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997;314:119. (11 January.)
2 Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine*. Edinburgh:Churchill Livingstone, 1997.

A crucial reference just missed being cited

EDITOR—The paper by P Moayyedi and colleagues continues the debate on whole blood testing for diagnosis of *Helicobacter pylori* infection, but it does not conclude it.[1]

A crucial reference which the authors could not cite because it was published a month after their paper was accepted indicates that experience elsewhere has been disappointing with the Helisal test, giving rates of false positive results of 33% and of false negative results of 25%.[2]

In addition, any financial benefits from screening for *H pylori* may take years to realise, if indeed they occur at all.[3]

Clinicians should always remember that half of the human race is infected by *H pylori*, without much evidence of adverse results for the majority. Conversely, eradication of *H pylori* is important in treating peptic ulcer and the rather rarer mucosa associated lymphoid tumour of the stomach. Treating mere dyspepsia with antibiotics is of uncertain benefit and could be disadvantageous.

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1 Moayyeddi P, Carter AM, Catto A, Heppell RM, Grant PJ, Axon ATR. Validation of a rapid whole blood test for diagnosing Helicobacter pylori infection. *BMJ* 1997;314:119. (11 January.)
2 Duggan A, Logan RPH, Knifton A, Logan RFA. Accuracy of near-patient blood tests for Helicobacter pylori. *Lancet* 1996;348:617.
3 Briggs AH, Sculpher MJ, Logan RPH, Aldous J, Ramsay ME, Baron JH. Cost effectiveness of screening for and eradication of Helicobacter pylori inmanagement of dyspeptic patients under 45 years of age. *BMJ* 1996;312: 1321-5.

Authors' reply

EDITOR—A Duggan and R Logan were concerned with our statement that the Helisal test had not been previously evaluated.

Their table shows a number of authors who have assessed the accuracy of the Helisal test, but these are all from abstracts or letters. To our knowledge this is the first peer reviewed paper reporting the accuracy of the Helisal rapid blood test. Their table shows wide variations in the specificity of the Helisal test.[1] One reason for this is that the gold standard used has been less than ideal in some cases. Another important reason why the accuracy of the Helisal test varies is that serology kits have different accuracies in different populations. This is especially important for near patient tests as cut off points cannot be tailored to suit the group being evaluated.

Duggan and Logan were also concerned about the details of the blinding used in our study. This was omitted owing to pressure of space, but all tests were carried out blind. All tests were also performed without knowledge of endoscopy results with the exception of the rapid urease test. The Helisal test was performed before endoscopy. The person performing the Helisal test was, of course, not blinded to the age and likely socioeconomic group of each patient, and this may have helped the investigator assign the correct *Helicobacter pylori* status when the Helisal test result was equivocal.[2]

R J Robinson and colleagues point out that the Helisal test is read subjectively and there is a 1% interobserver error. This is true of all subjective tests, not least histology for *H pylori* which is commonly used in clinical practice. It is important to be aware of interobserver error, but provided that it is low this should not preclude the use of the test in practice.

We agree with Brendan Delaney and colleagues that our conclusions may have been different in a general practice population. A modelling exercise has suggested *H pylori* screening may not be appropriate in young dyspeptic patients[3] but the validity of this model has been questioned.[4] These issues will be resolved only in well designed, randomised trials.

Brian T Johnston pointed out that the Helisal test would miss patients with oesophagitis. This is true, but endoscopy is also a very inaccurate method of diagnosing gastro-oesophageal reflux disease and we believe that in young patients it can usually be diagnosed on history alone.

Martin Dawes and colleagues and Catherine Hawke pointed out that we did not calculate likelihood ratios in our study. We agree that it would be useful to include likelihood ratios, but at the moment most clinicians are unfamiliar with this compared with more traditional methods of quoting accuracy. We hope in time that clinicians will become accustomed to likelihood ratios and their reporting will then become routine.

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2 Stone MA, Mayberry JF, Wicks ACB, Stevens M, Swann A, Robinson RJ. The Helisal test—an assessment of readability and diagnostic accuracy. *Gut* 1996;39(suppl 2): A110.
3 Briggs AH, Sculpher MJ, Logan RPH, Aldous J, Ramsay ME, Baron JH. Cost effectiveness of screening for and eradication of Helicobacter pylori in management of dyspeptic patients under 45 years of age. *BMJ* 1996;312: 1321-5.
4 Phull PS, Halliday D, Price AB, Jacyna MR. Absence of dyspeptic symptoms as a test for Helicobacter pylori eradication. *BMJ* 1996;312:349-50.

Interruption of methadone treatment by imprisonment

EDITOR—The number of opiate dependent drug injectors being prescribed methadone in Glasgow has risen 10-fold in the past five years and by the end of 1996 exceeded 2200. There is increasing evidence that this is helping many people achieve substantial improvements in health, social stability, and reduced criminality.[1] After several reports that methadone prescribing was being discontinued on imprisonment, we sent a short questionnaire in December 1996 to all 72 general practitioners in the Glasgow GP drug misuse clinic scheme.[2]

The 68 (94%) respondents were treating a total of 1866 patients with methadone. Of these, 276 had been imprisoned during the previous 12 months and a further 163 had been detained at least overnight in police custody. In only 11 (4%) and 4 (2.5%) cases respectively was there any communication between the prison doctor or the police surgeon and the general practitioner. Only 15 of the 276 prisoners had been given any methadone in prison.

Thirteen respondents described some benefits of imprisonment for a few patients, including improved physical health and abstinence from drug misuse, albeit usually short lived. However, 42 respondents reported adverse consequences of imprisonment for several patients, including severe symptoms of withdrawal, resumption of heroin injecting, needle sharing, and chaotic drug use both in prison and on release.

This survey has shown unacceptable discontinuity between clinical practice in the community and in prison, which seriously undermines the benefits to individual people and to the community of controlled methadone prescribing. There is an urgent need to improve communication between doctors in the prison and in the community. Procedures should be established to enable at least short term prisoners to continue successful treatment with methadone if this has the prescribing doctor's support.

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1 Macleod J, Scott R, Elliott L, Gruer L. The routine use of the opiate treatment index in the clinical setting. *Int J Drug Policy* 1996;7:130-1.
2 Scott R, Gruer L, Wilson P, Hinshelwood S. Glasgow has an innovative scheme for encouraging GPs to manage drug misusers. *BMJ* 1995;310:464-5.

Major journals should peer review trials at protocol stage

EDITOR—Increasing concern over the poor quality of medical research, and particularly over the conduct of clinical trials, has been voiced by the editors of the major medical journals. This unease has taken expression in the form of the CONSORT statement,[1 2] which states the criteria by which a trial should be judged. Unfortunately, most trials are not vigorously assessed until their results are submitted to a journal for publication—a time when it is too late for any errors in trial design to be remedied. There is also the second major problem of negative publication bias, whereby, perhaps unintentionally, it is easier to get the results of a trial published if the effect of treatment was positive than if it was not.[3]

We would like to propose a solution to both problems. We suggest that the major journals, such as the *BMJ*, should peer review trials at the protocol stage. If the trial design passes peer review as being timely, well designed, and of sufficient power for a negative finding to be of value then the journal should undertake to publish the trial report—even if the finding is negative. By this method journals would be able to exercise control over trial design at a stage where it could be appropriately modified and any subsequent negative publication bias would be prevented (something that most authors would welcome). A further potential benefit is that it would be only a small step to allow accepted protocols to be registered, thereby allowing other investigators to know what is happening elsewhere and so prevent duplication of effort.

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1 Altman DG. Better reporting of randomised controlled trials: the CONSORT statement. *BMJ* 1996;313:570-1.
2 Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996; 276:637-9.
3 Begg CB, Berlin JA. Publication bias: a problem in interpreting medical data (with discussion). *J R Stat Soc A* 1988;151:419-63.

⁂We have twice discussed whether we should peer review protocols for clinical trials. Both times we decided against for the following reasons.

Firstly, we fear that reviewing protocols may reduce the quality of the service we can offer to authors of completed papers. We receive about 5000 papers a year, and we have to work hard to reach our targets of giving authors of papers that we externally review an opinion within eight weeks and authors of papers we don't externally peer review an opinion within two weeks. Peer review of protocols would have to be followed by peer review of the completed papers. Such a system would thus substantially increase our workload, and we could cope only by substantially increasing our capacity for peer review.

All this might be acceptable if there were no bodies for reviewing protocols for clinical trials. There are, however, many such bodies. Mostly they are funding bodies, but protocols are also reviewed by ethics committees. A huge amount of academic time is already spent in peer review, and we don't think that further duplication of effort would be in the interest of science.

We may of course be wrong, and we are always willing to think again about any issue.—EDITOR

Managing measles

Size of infecting dose may be important

EDITOR—In describing severe measles one of us (DCM) made the error of linking the severity directly with the state of nutrition of the child when he or she contracted measles.[1] Several studies have since convincingly shown that the state of nutrition is unimportant, although vitamin A deficiency may play some part. The severity of measles was related to the degree of exposure, which was presumably related to the size of the infecting dose.[2] Analysis of patients' records from a severe outbreak of measles in Copenhagen in the past showed a similar finding.[3] Perhaps the size of dose may vary with the nutritional state of the child passing on the infection.

In his editorial Greg Hussey did not mention these findings.[4] If the case fatality rate and the severity vary by more than 100-fold between west Africa and Europe this should be worthy of further research to identify whether the degree of exposure and the size of the infecting dose are important in other infections. Perhaps people working in veterinary medicine may be able to help.

Should health workers in developing countries advise mothers to keep other, particularly small children, in separate beds (and where possible in separate rooms) from children who may be incubating or in the early stages of measles and possibly other infections? In Guinea-Bissau it was found that the number of people in the bed was a risk factor for childhood mortality (mortality ratio 1.37 (95% confidence interval 1.04 to 1.81)) when factors such as the number of children in the household, maternal education, sex, age, ethnic group, immunisation, presence of a bathroom, and absence of pigs in the household were controlled for.[5]

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Crystal violet and eye pads should not be recommended

EDITOR—Evidence based medicine is fine until we realise just how many of the many things that we order for our patients every day are untested and may never be tested. For example, I have two objections to the advice given by Greg Hussey in his editorial on managing measles.[1] Firstly, he recommends using gentian violet (crystal violet) in the mouth. *Martindale: the Extra Pharmacopoeia* gives a low rating to crystal violet as an antibacterial, and crystal violet can itself cause ulceration in the mouth and oesophagus.[2] Nor is crystal violet recommended in the *British National Formulary*.[3] Unfortunately, it is cheap and widely available in developing countries. It is painted on anything that looks diseased, especially burns. This prevents proper assessment of what is going on underneath. Probably its sole indication is for candidal infection when more expensive drugs are not available. Chlorhexidine can be made into a simple, colourless mouthwash, but saline or plain water is probably all that is needed. Secondly, Hussey recommends eye pads. I think that ophthalmologists will agree that eye pads wrongly applied and poorly supervised can be much more destructive to the eyes than fresh air. They also waste precious time, bandages, and dressings, and if applied to both eyes they probably frighten the child unnecessarily. With "measles eyes" already at risk of ulceration, eye pads may just finish the job.

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Giving paracetamol for fever is unnecessary

EDITOR—In his editorial Greg Hussey advises giving paracetamol if the temperature exceeds 39°C as one of the basic management principles when patients are admitted with measles.[1] The common understanding of the general public seems to be that when fever gets too high it can cause death. In hospitals this seems to be confirmed, because paracetamol is given when a patient has a fever. I have not, however, seen a publication to support this. This misunderstanding has major implications for general practice. A paper by Kai illustrates this.[2]

Current understanding is that people die of the underlying illness, not of fever. To support the benefit of fever one can start with the evolutionary argument. If fever was not of value for survival it would not be part of our defence. Research has shown that many immune responses are enhanced by an increase in temperature. Routine antipyretic treatment for fever is generally unnecessary and conceivably harmful.[3] It has been suggested that it may prolong illness and increase or prolong viral shedding.[4]

Parents do not need to worry about febrile convulsions, because when they telephone for advice the fever is already established and the episode of a rapid rise in temperature will have passed. Febrile convulsions, understandably, distress parents, but parents can be reassured that convulsions will not cause a disability. Also, the outcome is determined more by the underlying cause than by the seizures themselves.[5]

In conclusion, and in line with the views of Styrt and Sugerman, I would like to see routine antipyretic treatment reassessed and adjusted, depending on whether desired objectives (such as reduction of cardiovascular stress and increase in comfort) are being achieved.[3]

I think that paracetamol should be taken off the market. In 1994 the national measles and rubella immunisation campaign was instituted to prevent an expected 50 deaths, mainly among secondary school children. Comparison of this number with the annual number of deaths from paracetamol overdose in Britain (200) indicates that paracetamol should be taken off the market as a similar precaution. If this was done to coincide with a national campaign explaining the benefits of fever then it would have a major educational effect on the general public. Consequently, this would reduce the number of consultations in general practice considerably and would probably enhance the health of the nation.

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Author's reply

EDITOR—D C Morley and P Aaby highlight the infecting viral dose and crowding as the most important determinants of mortality. My editorial emphasised that severe disease should be expected in children with severe malnutrition, which is recognised to be an important risk factor for severe and fatal diarrhoea or pneumonia.[1] Diarrhoea and pneumonia are the main complications in children with measles. It would be expected that malnutrition may contribute to excess morbidity and mortality related to measles. Hospital based studies have indicated an association (not necessarily a causal one) between severe malnutrition and complications and death in children with measles.[3]

I agree with Ian Kennedy that the therapeutic benefit of crystal violet in the treatment of mouth ulcers has not been subjected to rigorous scientific evaluation. At a recent meeting on clinical research in the treatment of measles organised by the World

Health Organisation, the aetiology and management of mouth ulcers, including the use of crystal violet, was identified as a priority for further study.[3] Herpesvirus infection, candida, and other bacteria probably have a role. There is some evidence that crystal violet exhibits activity against skin bacteria and candida and may reduce morbidity in situations where more expensive therapeutic options are not available.[4] It is preferable to use a 0.25-0.5% concentration of crystal violet to minimise possible side effects. My recommendation about protective eye pads was that a pad should be applied only if there is evidence of vitamin A deficiency such as corneal ulceration. In such instances, if correctly applied, an eye pad will prevent the child from rubbing the eye and preclude further damage to the eye and secondary infection.[5] An eye pad is certainly not recommended for uncomplicated "measles eyes."

I note Wouter H Havinga's concerns about the use of paracetamol. The management of fever in children in developing counties has been critically evaluated by the World Health Organisation, which has recommended that paracetamol should be used only when the rectal temperature exceeds 39°C. If paracetamol is prescribed parents must be advised about its correct administration to prevent overuse.

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Elimination of firearms would do little to reduce premature deaths

EDITOR—John Gunn and colleagues suggest that doctors should be working towards the elimination of all firearms on the grounds that their removal would make an important contribution in reducing premature deaths.[1] The medical profession prides itself on doing thorough research before introducing new drugs or methods. I therefore suggest that, before it embarks on any campaign, it looks at the size of the problem. In evidence to the Cullen inquiry the Home Office reviewed all homicides in England and Wales during 1992-4.[2] Of a total of 2086 homicides, 196 were carried out with firearms. Of the 152 firearms that could be identified, 22 were legally owned, seven were believed to have been stolen from legal sources, and one was used by a member of the family of someone who owned it legally. An undisclosed subset of these firearms originated in the armed services. Thus at most a fifth originated from all legal sources. Most (at least 18) of the homicides were domestic. Outside the home the use of legal firearms is much lower, and the police have accepted a figure of 4% of all armed crime.[3] The table shows the annual number of deaths from various causes in England and Wales, taking the worst possible figure for legal firearms (that is, $(196/3) \times 20\%$).

Table 1 Number of deaths from various causes in England and Wales; worst possible figure for legal firearms was taken

Cause	No of deaths
Related to smoking (estimated)[4]	110 000
Road traffic accidents[5]	3213
All firearms	65
Legal firearms	13

The medical profession has clearly been correct to campaign against smoking. Firearms are understandably emotive, but I suggest that their elimination would not make an important contribution in reducing premature deaths. The elimination of legally held firearms "surplus to domestic and industrial requirements," as proposed by the authors, would be even less rewarding. Also, given that nearly a million people in Britain have legal firearms, any further controls are likely to be costly and counter productive.

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Severe persistent visual field constriction associated with vigabatrin

Chronic refractory epilepsy may have role in causing these unusual lesions

EDITOR—T Eke and colleagues report three cases of severe, symptomatic constriction of the visual fields associated with vigabatrin treatment.[1] We have had experience of a similar case. A 34 year old man who had had refractory partial onset seizures since the age of 8 was taking vigabatrin 3000 mg daily (since 1989), carbamazepine 1200 mg daily, and sodium valproate 5000 mg daily (both since 1982) when he suddenly developed visual deterioration with blurring and loss of peripheral vision in July 1995.

Surface electroencephalography suggested a left hemispheric focus, but magnetic resonance imaging of the brain showed no abnormality. On examination he had impaired visual acuity, with corrective lenses to 6/9 in both eyes. Pupillary responses were normal and confrontation visual fields full. There was pronounced bilateral optic atrophy and a maculopathy, both more evident in the right eye. His electro-oculogram was flat, and he had subnormal cone and rod electroretinograms. Visual evoked responses were normal. Vigabatrin was stopped, but his damaged retinal pigment epithelium and photoreceptors did not improve.

Vigabatrin was licensed in Britain and the Republic of Ireland in 1989; these were its first markets.[2] The mechanism by which the drug might produce retinal damage is unknown, and the symptoms did not improve in this patient when the drug was withdrawn. In addition, all of the patients reported on were taking other antiepileptic drugs at presentation. Our own patient had been treated previously with phenytoin, primidone, and lamotrigine. Chronic refractory epilepsy may also have a role in causing these unusual lesions. For example, disseminated intravascular coagulation associated with prolonged seizure activity may have been responsible,[3] rather than a toxic effect of lamotrigine.

Although it is reasonable to recommend ophthalmological review in patients with visual symptoms taking vigabatrin, we are still a long way from establishing a causal relation between long term treatment with the drug and retinal damage. Research is required to clarify the relation between visual disturbances, epilepsy, and antiepileptic drug treatment.

We thank Dr John Dudgeon for undertaking the ophthalmological examination in our patient.

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Reaction might be dose dependent

EDITOR—We have been conducting a systematic observational study of the long term efficacy and safety of the new antiepilepsy drugs gabapentin, lamotrigine, and vigabatrin; background information can be found in a recent letter.[1] Three cases of constriction of the visual field associated with vigabatrin, reported by T Eke and colleagues,[2] prompted us to review the results of our study. Seven hundred and thirteen patients who had been exposed to vigabatrin are included in this study, and one case of suspected constriction of the visual field associated with vigabatrin was seen. The patient was a 44 year old man with cryptogenic focal epilepsy, who started taking vigabatrin in November 1987 on a named patient basis. In August 1992 he complained that he kept bumping into

things, so he was referred to an optician and found to have restricted temporal vision fields. He was then referred for an ophthalmological opinion.

The ophthalmological tests confirmed marked constriction of visual fields and optic disc pallor, and the results of electrodiagnostic tests were similar to those in the cases reported by Eke and colleagues (details are available on request). It was thought that this could be an adverse reaction to vigabatrin because no other cause of visual field constriction could be found, and withdrawal of the drug was recommended. Owing to good control of his seizures, however, vigabatrin was reduced only from 4000 mg to 2000 mg daily. Further review suggested that the condition was stabilised after this reduction of the dose; therefore vigabatrin was not withdrawn, and regular review by the ophthalmologist confirmed no further deterioration of the condition after four years but no improvement either.

This patient's clinical picture is similar to that in the cases reported by Eke and colleagues. As vigabatrin was not stopped and the condition was stabilised after reduction of the dose, however, the reaction might be a type A reaction (that is, dose dependent). Therefore, Eke and colleagues may uncover the underlying mechanisms in their current study.

The manufacturer of vigabatrin suggested that reports of visual field problems in patients treated with vigabatrin seem to be rare, with a frequency of less than 0.1%.[3] In our study only one case was reported out of 713, and this suggests that the incidence is around 0.14%, which is of the same order of magnitude. The low incidence and long latency could explain why clinical trials fail to detect this possible adverse drug reaction. These cases seem to support Mignot's concern that studies are required to investigate the long term effects of the new drugs.[4]

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Patients taking vigabatrin should have regular visual field testing

EDITOR—We were interested to read T Eke and colleagues' report on three patients with constrictive field loss associated with vigabatrin.[1] A 30 year old photographer complained of progressive loss of peripheral vision over 12 months; he said that he bumped into people in crowded shopping centres. He had had complex partial seizures for 13 years with inadequate control until vigabatrin had been added to sodium valproate two years previously. Ophthalmological examination showed normal pupils, discs, and retina with normal retinal vessels. Computed tomography and magnetic resonance imaging of the head gave normal results, as did electroretinography and electro-oculography. A drug effect was suspected on the basis of exclusion, and the vigabatrin was stopped.

Vigabatrin most probably caused this patient's symptoms, even though perimetry showed changes less severe than those reported by Eke and colleagues. In view of the seriousness of this symptom and its failure to resolve when vigabatrin is stopped, we propose that all patients taking vigabatrin should have regular visual field testing, just as patients who are prescribed chloroquine in rheumatological practice have regular ophthalmological review.

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Four possible explanations exist

EDITOR—I can confirm the veracity of T Eke and colleagues' finding regarding visual fields.[1] The tests have been repeated in this department on the same patients with essentially similar results. Additionally, colleagues and I have examined two patients from the Birmingham area, who have yielded similar results. We were unable to confirm the abnormalities on electrophysiological testing, and none of the patients showed abnormalities on either electro-oculography or electroretinography.

Several possible explanations for the constricted fields remain. Visual disorders have been reported in patients receiving antiepilepsy drugs, and visual field disorders have been associated with both phenytoin and diazepam.[2 3] In addition, carbamazepine and phenytoin affect retinal function, reducing b wave amplitude and oscillatory potentials on electroretinography (A Bayer et al, spring meeting, Association for Research in Vision and Ophthalmology, Florida, 1990). These authors found that adding vigabatrin resulted in a return to normal threshold and improvement in b wave amplitude. Colleagues and I have confirmed this change when vigabatrin is added to patients receiving carbamazepine and other antiepilepsy drugs. It is clear that several antiepilepsy drugs may be implicated in constrictions of the visual field and reduced retinal function. Vigabatrin produces microvaccuolation in the myelin sheath of dogs and rodents but not in humans or monkeys.[4]

Vigabatrin (γ-vinyl-aminobutyric acid) inhibits the action of γ-aminobutyric acid transaminase and results in increased persistence of γ-aminobutyric acid. It may have systemic effects other than its intended mode of action in the brain. γ-Aminobutyric acid is found in the retina,[5] lateral geniculate nucleus, and visual cortex. It mediates lateral inhibition in the retina, but why this should cause constriction of the visual field and not an increase in overall threshold is unclear. In the visual fields that we assessed no such overall effect was observed. Possibly, however, the density of retinal ganglion cells is a critical factor. If changing the persistence of γ-aminobutyric acid does turn out to be critical then all antiepilepsy drugs using this mode of action should cause similar effects.

There are four possible explanations: abnormal visual fields are associated with a history of complex partial seizures; vigabatrin and other drugs increase the persistence of γ-aminobutyric acid, causing visual field constriction by some unknown mechanism; carbamazepine and other antiepilepsy drugs cause the changes; and vigabatrin in association with other antiepilepsy drugs produces the changes. It is not possible to exclude any of these options, and further studies, particularly on patients with complex partial seizures who have received vigabatrin in the absence of other antiepilepsy drugs (in particular carbamazepine) will be required.

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Manufacturers have started several studies

EDITOR—T Eke and colleagues report visual field abnormalities in three patients with epilepsy who were receiving vigabatrin concurrently with other antiepilepsy drugs.[1] We wish to discuss these reports in the light of our worldwide experience with vigabatrin, and to outline the continuing efforts that we have made to evaluate this issue.

Roughly 140 000 patients have been treated with vigabatrin since its introduction in 1989. During this period Hoechst Marion Roussel has received rare reports of visual field defects (frequency less than 0.1%), including the cases described by Eke and colleagues.

The key question raised by these reports is whether a causal association exists between the observed events and vigabatrin. Unfortunately, this question cannot be answered on the basis of the information provided in the case reports. As with other

reports that we have received, Eke and colleagues did not provide the results of baseline eye examinations. Consequently, it is not known if there was evidence of visual field defects before treatment with vigabatrin. Secondly, data obtained from the medical history, physical examination, and electrophysiological testing in all cases reported to Hoechst Marion Roussel have been reviewed by several academic experts in neuro-ophthalmology. All found the information to be inconsistent and in some cases conflicting, without any recognisable clinical picture. Finally, most reports occurred in patients with refractory seizure disorders receiving other antiepilepsy drugs. Visual field defects or retinal disorders have been described in patients with epilepsy[2] as well as with other antiepilepsy drugs,[3-5] which underscores the potential for confounding by either disease or other drugs.

Hoechst Marion Roussel is committed to evaluating any potential safety issues that may occur with its products. To address the limitations of the available information and to answer questions raised by the rare reports of visual field defects we have (1) added visual field examination and electroretinography to several clinical trials started within the past two years; (2) started a study to assess the pharmacological effects of vigabatrin on retinal function; and (3) started a study to define the epidemiology of visual field defects in patients with epilepsy treated with antiepilepsy drugs. While we await answers to these questions it seems prudent for clinicians to remain vigilant for the signs or symptoms of visual disturbances in all patients with epilepsy receiving any antiepilepsy drug.

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Swiss experience of managed care

Editor—Chris Ham's editorial on managed care in Europe ignores the Swiss experience.[1] Traditionally, Swiss citizens could see any doctor they wanted, paid the doctor on a fee for service basis, and were reimbursed by the health insurance company to which they belonged. In 1990, in an attempt to curb healthcare expenditure, the federal government authorised "health insurance contracts with limited choice of doctor" (which means health maintenance organisations minus the political marketing wrapping), and this option remained in the new Law on Health Insurance, adopted in 1994. Under this law, health insurance companies can offer cheaper contracts that limit the choice of providers, although the services covered must conform to a standard list.

At first, staff model health maintenance organisations were set up in Zurich and Basle, in which doctors and other staff who were hired received a salary. Networks of independent practitioners appeared next, in Winterthur and Geneva; these contract with insurance companies to provide all healthcare services to a defined pool of patients on a capitation basis. In Geneva such a structure was created in 1992, initially for the students and staff of the university. Doctors had to work within a capitated budget, and members of the plan paid lower premiums. With a few exceptions, members of the plan could consult only designated gatekeepers without prior approval. This plan benefited from favourable self selection: members who accepted the switch to the new system had used fewer health services in the previous year than those who refused.[2]

One year later the health status of members of the plan remained unchanged, but their satisfaction with health care received in the previous year had decreased.[3] Similarly, members of the plan who consulted gatekeepers were less satisfied with their visit than those who were referred to an independent specialist and less satisfied than patients in other health insurance plans who consulted a private group practice or at a hospital based outpatient clinic.[4] Dissatisfied members resented having gatekeepers imposed to them and considered that a normal relationship of trust could not properly develop.[5] The plan did, however, achieve substantial reductions in healthcare expenditure in its first year, even when account was taken of the favourable self selection (unpublished findings).

The latest managed care organisations in Switzerland resemble "preferred provider organisations," in which doctors agree to lower reimbursement fees but very little else is managed. Such organisations may be profitable because of the interplay of inequitable selection and hidden cost transfers between subgroups of patients. Unfortunately, the obligation to evaluate managed care plans disappeared in the law of 1994.

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WHO is producing a reproductive health library for developing countries

Editor—We agree with Neil Pakenham-Walsh and colleagues that lack of access to reliable, up to date medical information on effective treatments is one of the most important problems faced by health workers in developing countries.[1] To address this need in reproductive health we have initiated the World Health Organisation Reproductive Health Library project in collaboration with centres around the world and in association with the Cochrane Collaboration. Cochrane reviews are increasingly being acknowledged as a reliable source of evidence based information on healthcare interventions. The reproductive health library will contain, on one disk, a selected number of Cochrane reviews (25 in the 1997 disk) on topics of high priority for developing countries. A special feature of the library will be commentaries on the relevance of the reviews' findings to developing countries. These commentaries are being written by health workers in developing countries or by people with experience of living and working there. They are peer reviewed before being accepted for publication.

The WHO Reproductive Health Library will be published by the WHO annually, beginning in June this year, and will be distributed free to health workers in developing countries through the relevant mailing lists of the WHO and other agencies and networks around the world.[2 3] The library will be evaluated in studies to assess its impact on health practices in developing countries. Anyone who would like more information on the library, or who can contribute names and addresses of people in developing countries who may use the programme, is welcome to contact the address below.

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