unknown referee as any evidence of these could then be referred back to the referee's institution. The bench test of a piece of research is its shelf life: will it still be of interest or relevant in 10 years' time? This test could equally well apply to negative findings. Many important discoveries throughout history have initially been considered to be unacceptable on religious or cultural grounds. As the ultimate peer reviewer is the wider medical audience, the medical referee should perhaps just act as the referee without acting simultaneously as the goalkeeper, leaving readers and subsequent events to be the best judge of a paper's worth.

D N POLLER
Senior registrar

Gloucestershire Royal Hospital NHS Trust,
Gloucester GL1 3NN

1 Smith R. Promoting research into peer review. *BMJ* 1994;309:143-4. (16 July.)

Referees should provide references

EDITOR,—I applaud the *BMJ*'s efforts to improve the quality of the peer review process.¹ A small improvement would come if referees were under the same obligation as authors to provide references in support of statements drawn from the literature. A critical review should be a catalyst to renewed and improved effort. This is not the effect if an author is unable to trace the source of a reviewer's criticism; instead, the temptation is to question the motives or abilities of the reviewer and even to question the probity of the journal he or she represents. This should also apply to reviews of applications for research grants, when a vague, unsupported statement saying "something like this has been done before" will result in almost certain rejection.

If a reviewer is genuinely in a position to give an expert opinion the addition of references should mean little extra work. If a bibliographic database is used² there is even no need for extra typing.

PETER FURNESS
Senior lecturer

Department of Pathology,
Leicester General Hospital NHS Trust,
Leicester LE5 4PW

1 Smith R. Promoting research into peer review. *BMJ* 1994;309:143-4. (16 July.)

2 Jones RG. Personal computer software for handling references from CD-ROM and mainframe sources for scientific and medical reports. *BMJ* 1993;307:180-4.

The role of letters in reviewing research

EDITOR,—R S Bhopal and Alison Tonks have pointed out that the potential of material on the correspondence pages remains underdeveloped and undervalued.¹ An editorial by Charlton published in *Anaesthesia* included some letters to the editor without making any reference to those letters or their authors.² Charlton had been advised by the journal's editor that "it would not be normal to refer to the correspondence when referencing an editorial about a topic of major interest" (personal communication.) It is perplexing that recommendations published in correspondence can be used but their authors not credited. It is high time for the editors of the leading international scientific journals to formulate guidance for authors of articles and editorials so that they cite published correspondence when they use the message contained in such letters.

Letters to the editor that are in the form of suggestions or recommendations that do not necessarily comment on a published article should also be considered. Bhopal and Tonks also stated that if literature searches of published reports are to include relevant letters, corrections, and other

comments, then a system will need to be developed systematically and reliably to link papers with other relevant material; indexing of all letters to original research must be the first step. In my opinion such indexing should not be restricted to letters responding to original research: it should include other letters of wide interest. Implementing the suggestions put forth in such letters to the editor might be beyond the scope of an individual, demanding participation and commitment of institutions. Some authors might not be backed by fully equipped laboratories and other infrastructure to scientifically validate their ideas. Letters to the editor are one outlet for airing those ideas. These need encouragement, not reproach.

GOPIN KALLA
Anaesthesiologist

PO Box 101, KFMH,
Khamis Mushayt,
Saudi Arabia

1 Bhopal RS, Tonks A. The role of letters in reviewing research. *BMJ* 1994;308:1582-3. (18 June.)

2 Charlton JE. Checklists and patient safety. *Anaesthesia* 1990;45:425-6.

Statistics notes

Defining sensitivity and specificity

EDITOR,—In their statistics note on the sensitivity and specificity of diagnostic tests Douglas G Altman and J Martin Bland's idiosyncratic use of the term "true positive" is unconventional and unhelpful and will confuse readers.¹ Since 1947, when Yerushalmy introduced the terms sensitivity and specificity to aid understanding of the utility of diagnostic tests,² respected authorities on both sides of the Atlantic have used the term true positives to indicate those cases in which the disease is present and the diagnostic test gives a positive result.^{3,4} To use the term to mean all cases of the disease regardless of the test result is a redundancy, and to use it in this way when defining sensitivity and specificity further obfuscates what for several students and physicians (and perhaps statisticians?) is already confusing.

GORDON L DICKIE
Associate professor

Department of Family Medicine,
University of Western Ontario,
London,
Canada

1 Altman DG, Bland JM. Diagnostic tests 1: sensitivity and specificity. *BMJ* 1994;308:1552. (11 June.)

2 Yerushalmy J. Statistical problems in assessing methods of medical diagnosis, with special reference to x-ray techniques. *Public Health Rep* 1947;62:1432-49.

3 Rose G, Barker DJP. *Epidemiology for the uninitiated*. London: BMA, 1979.

4 Sackett DL, Haynes RB, Guyatt GH, Tugwell P. *Clinical epidemiology: a basic science for clinical medicine*. Toronto: Little, Brown, 1991.

5 Armitage P. *Statistical methods in medical research*. New York: Wiley, 1977:433.

Regression towards the mean

EDITOR,—J Martin Bland and Douglas G Altman's note on regression towards the mean fails to convey the process underlying the phenomenon except in mathematical terms.¹ I hope that the following account may make the relation between regression towards the mean and the correlation coefficient r more understandable.

Assume that there is perfect correlation between a child's height and the mid-parental height ($r=1$). Then one can predict, without error, the child's height from knowledge of his or her parents' height and vice versa. If the mid-parental height is above the mean then so will the child's be, by an equal amount. There is no regression to the mean.

On the other hand, assume that a person's height is completely unpredictable from knowledge of his or her parents' height. There is no correlation

between parental and child height ($r=0$). Tall parents will have had this unpredictable effect act in the direction of making them tall, but their children will have an equal likelihood of being tall or small. The mean height of the children of tall parents will be the mean height of all children. There is complete regression towards the mean.

In reality r lies between 1 and 0; there is a predictable component relating parental height to child height and, in addition, an unpredictable component. If a child's parents are tall then the likelihood is that the chance effect acted to increase the parents' heights above what would have been predicted. These chance effects are not heritable (by definition), and the child's height, on average, is therefore closer to the mean height of all children than the parents' heights are to the mean height of all parents. The larger the unpredictable component relative to the predictable component the smaller is r and the more likely it is that a person's height deviates from the mean because of chance effects. These unpredictable effects will not be seen in the relative whose height is closer to the mean. Therefore the smaller is r the greater is the regression to the mean.

SIMON FLEMINGER
Senior lecturer in psychiatry

Academic Department of Psychiatry,
London Hospital Medical College,
London E1 2AD

1 Bland MJ, Altman DG. Regression towards the mean. *BMJ* 1994;308:1499. (4 June.)

Authors' reply

EDITOR,—We agree with Gordon L Dickie that in the context of diagnostic tests the term "true positives" is usually used to mean those people with the disease in whom the diagnostic test gives a positive result. We think that our meaning was clear and hope that not too many readers were dismayed by our non-standard terminology.

Regression towards the mean is a difficult concept. We hope that *BMJ* readers will find Simon Fleminger's description helpful.

DOUGLAS G ALTMAN
Head

Medical Statistics Laboratory,
Imperial Cancer Research Fund,
London WC2A 3PX

J M BLAND
Reader in medical statistics

Department of Public Health Sciences,
St George's Medical School,
London SW17 0RE

Patients are unwilling to enter clinical trials

EDITOR,—T C B Dehn is right to draw attention to the problems of obtaining informed consent from patients entering randomised trials, particularly when one option entails additional, potentially toxic treatment, such as chemotherapy.¹ But Dehn's letter also illustrates the problem of avoiding bias when describing a trial: Dehn admits that five of six patients refused to enter a trial comparing preoperative chemotherapy with surgery alone for oesophageal cancer because of anxiety that they might get chemotherapy. I wonder if, had the patients been seen by an oncologist, a similar number might not have refused because they did not want to miss out on the "beneficial" effects of the chemotherapy.

A colleague and I are both committed to a particular trial testing the value of prophylactic cranial irradiation in small cell lung cancer. We both think that we are honest in our description of the hazards and benefits, and, while many of my patients refuse because they do not want the risk of toxicity, many of hers refuse because they do not

want to lose the benefits. It seems we are each unwittingly introducing a different bias by what we say.

If randomised clinical trials in cancer are to be successful in recruiting patients, clinicians need more guidance on what is meant by informed consent and how to obtain it. An article by Tobias and Souhami² and subsequent correspondence³ aired some of the issues but did not help with the practicalities. Perhaps the *BMJ* could commission a "How to do it" article—or is it too difficult?

FERGUS MACBETH
Locum oncologist

Christchurch Hospital,
Christchurch,
New Zealand

1 Dehn TCB. Treatment of oesophageal cancer. *BMJ* 1994;309:126. (9 July.)

2 Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. *BMJ* 1993;307:1199-301.

3 Correspondence. Informed consent in clinical trials. *BMJ* 1993;307:1494-7.

Advertisement for Zantac

EDITOR,—I am concerned by the advertisement for Zantac that has appeared in the *BMJ*.¹ It reads: "It's an effective treatment. Successfully healing both duodenal and gastric ulcers. But, used as prophylaxis, Zantac can actually prevent NSAID-associated duodenal ulcers. In fact it's the only H₂ licensed to do this."

The most likely site of any damage to the gastrointestinal tract associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) is the gastric mucosa and not the duodenum.² The *British National Formulary* states, "Therapy [with H₂ antagonists] can promote the healing of NSAID-associated ulcers but there is no proof that the ulcer complications are prevented."³ Zantac is licensed for prophylaxis against only duodenal ulcers associated with non-steroidal anti-inflammatory drugs. Why Glaxo was granted a licence so inappropriate and open to misinterpretation I can only wonder.

I am concerned that the wording of the advertisement implies that Zantac can be used for prophylaxis against all ulcers induced by non-steroidal anti-inflammatory drugs. If this was not so the advertisement would surely have mentioned only duodenal ulcers. In my opinion this advertisement has been phrased in such a way as to encourage the inappropriate use of a drug outside the terms of its product licence. I have expressed my concerns to the Medicines Control Agency.

FINDLAY M HICKEY
Pharmaceutical prescribing adviser

Grampian Health Board,
Aberdeen AB9 1RE

1 Advertisement for Zantac. *BMJ* 1994;309:between pages 96 and 97 (clinical research edition) (9 July.)

2 How often do NSAID-induced ulcers occur? *MeReC Bulletin* 1992;3:23.

3 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary number 27* (March 1994). London: BMA, RPSGB, 1994:33.

Manufacturer's reply

EDITOR,—The advertisement to which Findlay M Hickey objects promotes Zantac for the licensed indications of healing and preventing duodenal ulcers and healing gastric ulcers related to non-steroidal anti-inflammatory drugs (NSAIDs). Hickey's main objection seems to be based on his belief that Zantac should not have been granted a licence for the prevention of duodenal ulcer associated with non-steroidal anti-inflammatory drugs. He apparently believes that the section that he quotes from the *British National Formulary*

supports his contention that H₂ antagonists do not have a role in this indication. In fact, the sentence states that there is no evidence that they prevent the complications of peptic ulcers. Indeed, the formulary also states, "Treatment [with ulcer healing drugs] in patients taking NSAIDs may prevent the development of peptic ulcers but has not been shown to prevent complications of bleeding or perforation."¹ Clearly, therefore, Hickey has misunderstood this information.

To extend a product licence it is necessary to satisfy the Medicines Control Agency that there is sufficient evidence of efficacy for a new indication. This has been achieved with regard to the use of Zantac 150 mg twice daily with non-steroidal anti-inflammatory drugs in the prevention of duodenal ulceration but not in the prevention of gastric ulceration; hence the specific indication of duodenal ulcer.

The separate indications of prevention and healing are clearly stated in the text of the advertisement: "Successfully healing both duodenal and gastric ulcers. But, used as prophylaxis, Zantac can actually prevent NSAID-associated duodenal ulcers." In addition, the indications are clearly spelt out in the indications section of the prescribing information in the advertisement and are further qualified in the precautions section. We therefore see no grounds for the allegation that the advertisement implies that Zantac can be used for prophylaxis against all ulcers induced by non-steroidal anti-inflammatory drugs or encourages inappropriate use of the product outside the terms of its licence.

Although pharmaceutical companies are not required to substantiate the validity of indications in product licences, references to published studies appear in the advertisement for Zantac and we would be happy to provide them to Hickey or any other appropriately qualified person on request.

DARRALL L HIGSON
Associate medical director

Glaxo Laboratories,
Uxbridge,
Middlesex UB11 1BT

1 British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary number 27* (March 1994). London: BMA, RPSGB, 1994:33.

Experimental and observational methods of evaluation

EDITOR,—Trevor A Sheldon's editorial perpetuates the false dichotomy between experimental and observational research.¹ Once again an advocate of randomised controlled trials seeks to discredit evaluative research that uses observational data as if the two methods were alternatives rather than complementary approaches. Extremist supporters of either camp offer unacceptably simple accounts.

Of course in some people's ideal world every intervention in the biological and social spheres would be evaluated with a randomised controlled trial. But the world is not such a utopia. As a consequence there are important roles for observational methods used with the care and rigour that, hopefully, trialists bring to their studies. What are those roles?

Firstly, some interventions, such as defibrillation for ventricular fibrillation, have an impact so large that observational data are sufficient to show it.

Secondly, infrequent adverse outcomes would be detected only by randomised controlled trials so large that they are rarely conducted. Observational methods such as postmarketing surveillance of medicines are the only alternative.

Thirdly, observational data provide a realistic means of assessing the long term outcome of interventions beyond the timescale of many trials. An example is long term experience with different hip joint prostheses.

Fourthly, whatever those who question the value of health care interventions might think, many clinicians often will not share their concern and will be opposed to a randomised controlled trial; observational approaches can then be used to show clinical uncertainty and pave the way for such a trial.

Fifthly, despite the claims of some enthusiasts for randomised controlled trials, some important aspects of health care cannot be subjected to a randomised trial for practical and ethical reasons. Examples include the effect of volume on outcome, the regionalisation of services, a control of infection policy in a hospital, and admission to an intensive care unit. To argue that these topics could theoretically be evaluated by a randomised controlled trial is of little practical help in advancing our knowledge.

Why advocates of trials feel the need to criticise the use of non-experimental methods is unclear. After all, randomised controlled trials have their limitations. Evaluation would benefit if everyone recognised and appreciated the vital and complementary roles that experimental and observational methods have.

NICK BLACK
Reader in public health medicine

Department of Public Health and Policy,
Health Services Research Unit,
London School of Hygiene and Tropical Medicine,
London WC1E 7HT

1 Sheldon TA. Please bypass the PORT. *BMJ* 1994;309:142-3. (16 July.)

Inventing a new diagnostic test

EDITOR,—I was most interested in the article by Tom O'Dowd and Nick Bourne about their experience in technology transfer from university to industry.¹ They failed to mention how they handle the problems of indemnity against product liability and proof of intellectual property rights and how they and their industrial partners share this. It would be most helpful if they could give us the benefit of their experience on these issues.

PETER SÖNKSÉN
Professor

Division of Medicine,
St Thomas's Hospital,
London SE1 7EG

1 O'Dowd TC, Bourne N. Inventing a new diagnostic test for vaginal infection. *BMJ* 1994;309:40-2. (2 July.)

Authors' reply

EDITOR,—We agree with Peter Sönksen that universities need to make sure that they have their act together in the complex world of exploiting medical research. He asks two important questions, on product liability and on proof of intellectual rights.

Under the terms of our arrangement, our licensee was required to indemnify us against product liability claims against third parties. It is advisable actually to see a copy of the licensee's insurance cover to assess its extent. Such indemnities can prove extremely expensive in litigious territories like North America.

We were licensing an idea, which was worked up to the stage of prototype kit. We did not actually license a product, but an idea on which the company itself would base a future product. It is important that the company makes its own assessment of the technology to ensure its "fitness for purpose." As a further precaution the licensee should make a "no warranty" statement in the licence agreement. Our experience indicates that commercial partners see such precautions as good business and indeed sound investment.

As to proof of intellectual rights, a licensor of a