CORRESPONDENCE

Because we receive many more letters than we have room to publish we may shorten those that we do publish to allow readers as wide a selection as possible. In particular, when we receive several letters on the same topic we reserve the right to abridge individual letters. Our usual policy is to reserve our correspondence columns for letters commenting on issues discussed recently (within six weeks) in the BMJ.

Letters critical of a paper may be sent to the authors of the paper so that their reply may appear in the same issue. We may also forward letters that we decide not to publish to the authors of the paper on which they comment.

Letters should not exceed 400 words and should be typed double spaced and signed by all authors, who should include their main degree.

Bias in awarding research grants

SIR,—Dr Brian Martin makes serious allegations against the National Health and Medical Research Council (NHMRC) of Australia (30 August, p 550). The context is the protracted correspondence between Dr Eva Wertheim (referred to as Dr Smith), the NHMRC, and the Commonwealth ombudsman about Dr Wertheim's unsuccessful grant applications. I am taking issue not with Dr Wertheim but with Dr Martin for the allegations of injustice, bias, misrepresentation, and falsification he makes against the NHMRC.

The case can be summarised as follows. From 1976 to 1982 project grants were rated from 1 (poor) to 6 (excellent) by two anonymous external assessors and the applicant interviewed by a multidisciplinary regional committee, which scored each project from 1 to 6 on the basis of application and interview. Dr Wertheim applied for project grants in 1976, 1979, and 1982. When the 1976 application was not funded she requested—as is her right—a commentary from the NHMRC on her application and interview. She was happy with neither the verdict nor the NHMRC response. In 1979 her application succeeded, in 1982 it was unsuccessful, as was her application for an NHMRC fellowship. Under the newly introduced Freedom of Information Act she sought documentation of her rejected grants. Among the documents was one in which an assessor's rating had been incorrectly entered on a committee member's report form.

Dr Martin says, "Although it seems certain that an injustice was perpetrated [in Dr Wertheim's case], there is no way to prove bias." The qualifier is unsustainable and the main clause misleading. Dr Wertheim, appropriately in my opinion, not satisfied with the responses she received from the NHMRC, took her case to the ombudsman. He found that various NHMRC procedures were suboptimal (and that they have since been much improved); he criticised aspects of the way the complaint had been handled but found no evidence of injustice. There are ways in which bias can be strongly suspected on a population basis, if not proved in an individual case. If proposals written by women are much less successful than those written by men, those written by people with Central European names less (or more) successful than those written by Smith or Jones, those written by PhDs less successful than those written by medical graduates, then various sorts of bias—gender, ethnic, or clinical—may be entertained. The possibility of such biases can be examined in the NHMRC system; and until such an examination is made, and dispassionately reported, the statement that bias exists is nothing more than prejudice or spleen. In fact Dr Wertheim was successful in one out of three applications, which is almost exactly the average success rate for project grant applications in 1976-82.

Dr Martin claims, "It seems reasonable to infer that the spokesman [of the committee considering Dr Wertheim's application] misrepresented the assessors' reports to the committee." The inference here is that only the spokesman saw the external assessors' report. This is not the case; applicants for grants are interviewed by a committee, all members of which can make their own judgments on the assessors' reports. Clearly, the spokesman did not agree with one assessor who rated the project as 5/6 ("very good"); equally clearly, his opinion was shared by every other member of the interviewing committee.

Dr Martin says, "One assessor's rating was altered from 5 to 1." This refers to an error made by the spokesman, who entered 1 rather than 5 in the box reserved for the assessor's mark. To alter a rating from 5 to 1 would have entailed tampering with every copy of the assessor's report, in which the box marked 5 had been ticked; proof that the assessor's rating was not altered is that the entry on the spokesman's report could be shown to be wrong. The ombudsman makes clear that the erroneous entry had no bearing on the fate of the application.

The NHMRC, as a committee of the Department of Health, has no corporal voice; as an individual I have tried to point out the groundlessness of Dr Martin's charges. I have never been a member of NHMRC; I have served on interviewing committees and have had grant applications approved and rejected over the period in question. I share with Dr Wertheim the feeling of dismay and disbelief when an application fails; I do not, however, share with Dr Martin the feeling that this reflects injustice, bias, and falsification by those responsible for the negative decision, in a system where on average only one application in three is funded.

In his discussion Dr Martin puts the specific charges into the wider context of peer review performed in secrecy by anonymous elites with unspecified (but five times reiterated) vested interests. Open institutions—like democratic government and peer review—are fertile ground for conspiracy theories; in closed societies the enemy is obvious, and there is no need to postulate any hidden forces to explain lack of success. The NHMRC system of peer review and awarding research grants is imperfect, like any human institution. The system was substantially refined between 1976 and 1982 and recently has become even more "user friendly." It still has some (little) way to go—for example, by providing the assessors' reports to applicants before interview. All this aside, it has emerged as a democratic and externally accountable method of ranking competing project grants in a situation where funding has been scanty and competition for limited funds fierce.

Dr Martin asks that "The discussion should encompass not only administrators and scientists but also members of the general public, all of whom have a stake in fairness and the promotion of scholarship in service to the community." Quite so; but the promotion of scholarship is not served by innuendo and insupportable allegations of injustice—all of which have been examined and dismissed by the office of the ombudsman.

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SIR,—I read with interest and concern the paper by Dr Brian Martin (30 August, p 550). He makes

some important points about the weakness of the peer review process associated with the funding of research grants, both in Australia and in other countries. I believe that any process of review will have faults and the important question is whether there is likely to be an improvement if the changes he suggests were implemented.

I read with concern because some of the statements made by the author appeared to be as unscientific as he claimed some of the grant reviewers' conclusions have been. Firstly, he states, "It seems reasonable to infer that the spokesman misrepresented the assessor's reports to the committee." This suggests that the author does not understand the way in which the committee functions. I have applied for grants and have been interviewed by committees which were composed of individuals all quite capable of making a personal assessment of the grant before them and of the grant applicant at the time of interview. While I am not a member, nor have I been, of any of the National Health and Medical Research Council review committees I find it impossible to believe that any of the spokespeople could influence a committee of six or seven to rate a project less than 1 unless there were some very good reasons for so doing.

The second unscientifically validated statement, "that the PhD versus MD issue within the medical research community symbolises a number of differences that are often keenly felt," appears to be made as an explanation for the difficulty experienced by Dr Smith in obtaining funding for the grant. As someone who has worked with people with MDs and those with PhDs for many years I find this statement so far from a reasonable statement of the position in Australia that I wonder how it could have been made by an academic seeking to help the development of our research funding process. As to whether women are treated more harshly than men when it comes to the awarding of grants I think we need evidence rather than unsubstantiated statements.

I believe Dr Martin does raise very important issues about the peer review process but I wonder whether removing anonymity would lead to a less critical system than we presently have, to the detriment of the overall standard of grants funded.

While it would be reasonable to believe that in Australia one could make scientifically critical statements as a reviewer without implications for one's own grant applications there are many who might lower the standard of criticism of an application, thus defeating one major purpose of the external review—that is, clear scientific criticism of a research proposal. This acknowledges that human foibles do influence our review process.

In Australia the medical research budget is significantly lower than that in most developed countries. There are always more grant applications than there are funds to award. Thus many excellent projects remain unfunded each year through sheer lack of funds. It would seem that the example quoted by the author was an unfortunate one to pick, in that while one reviewer did award the grant a mark of 5 it was clear that other individuals did not find it worthy of funding. It is possible that in 1976 even if the grant had been felt by a number of individuals to have been fair to good it would not have received funding because of the small research budget available. Although Dr Martin is endeavouring to challenge us in our thinking about the awarding of research grants, he has done the situation a disservice by not researching it as adequately as he might have.

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Relapse of duodenal ulcer

SIR,—Dr J Paul Miller and Mr E Brian Faragher concluded their leading article (1 November, p 1117) with the recommendation that the reported observations (and inferences therefrom) "should probably influence prescribing." Right, but how?

There are clearly two problems associated with current ulcer healing therapy. Firstly, most ulcers relapse if treatment is stopped. Even if the ulcers healed by H_2 blockers relapse more rapidly (and no generalisation is possible from currently available data), nearly two thirds of patients treated with tripotassium di-citrato bismuthate (De-Nol) relapse within one year of healing. As we have pointed out,[1] all (and any) ulcer relapse may present with a complication, and in one recent study the rate of complication during ulcer recurrence was over 15% in six years and 30% if patients had previously suffered from a complication.[2] Since any complication may be lethal, we have concluded that it is not permissible to allow any ulcer to relapse, since it is not possible to predict which relapse is going to be dangerous.

Secondly, all relapses have to be retreated, time after time. Cimetidine and ranitidine have been used for repeated, or continuous, treatment for 10 and five years respectively and even in animals have not produced significant long term adverse effects. Information about the effects of repeated or long term treatment with the current bismuth containing preparations is not available either in man or in animals. Experience with earlier bismuth containing antiulcer drugs was unsatisfactory since some patients developed encephalopathy or arthropathy. It is not valuable to state that a drug "is recommended for four to eight week courses" when it has previously been stated that at least 59% of treated patients relapse within one year and will therefore require retreatment within a year. With which drug? And what about next year? And the year after that? How much bismuth is going to have accumulated after a few years of repeated treatment? We do not know and I am not prepared to risk the matter in my patients with ulcers.

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1 Boyd EJS, Wormsley KG. Natural history of duodenal ulcer. *Survey of Digestive Diseases* 1985;3:230-9.
2 Elashoff JD, Deventer G van, Reedy TJ, *et al.* Long-term follow-up of duodenal ulcer patients. *J Clin Gastroenterol* 1983;5: 509-15.

AUTHOR'S REPLY—The conclusion from Dr Wormsley's statement that "it is not permissible to allow any ulcer to relapse" is that every patient with duodenal ulcer should at the time of diagnosis be put on to lifelong maintenance treatment or undergo surgery. This may be reasonable in certain high risk groups, but this policy has not been generally adopted among gastroenterologists. The H_2 antagonists currently in wide use are both excellent drugs with very good safety records, but we do not yet know what the risk-benefit ratio would be from their universal continuous use over decades.[1] For these reasons I prefer to reserve permanent maintenance for the patient who has proved that he rapidly relapses and for high risk patients—for example, the elderly with other medical problems. Moreover, it is not possible with any available treatment to prevent all relapses. On long term H_2 blockade the annual relapse rates are between 10 and 47%, though I would accept that such relapses are rarely accompanied by complications.

Bismuth encephalopathy was associated with the prolonged use of high doses of insoluble bismuth salts.[2] It is apparently reversible and has never been described with a daily ingestion of less than 1·5 g bismuth metal. It has never been described with tripotassium di-citrato bismuthate (De-Nol) in recommended doses, and more than 1·5 million treatments have been dispensed. The recommended daily dosage of tripotassium di-citrato bismuthate contains 480 mg bismuth. It has been proposed that bismuth preparations should be discontinued if blood concentrations exceed 100 µg/l, with 50-100 µg/l being considered as an "alerting zone."[3] Patients with encephalopathy have generally had levels of several hundred or several thousand µg/l, while in nearly 500 patients given therapeutic doses of tripotassium di-citrato bismuthate the mean level was 7·0 µg/l with only two values in the alerting zone (Bader JP, De-Nol Symposium, Sao Paulo, 1986). A simple way of estimating tissue bismuth concentrations is, however, clearly desirable.

Tripotassium di-citrato bismuthate is not recommended for long term maintenance, but a maintenance trial is in progress to assess its safety and efficacy from this viewpoint (Porro GB, De-Nol Symposium, Sao Paulo, 1986). It takes about two months for urinary bismuth values to return to pretreatment levels after a course of tripotassium di-citrato bismuthate, leading to the suggestion that there should be a two month period between successive courses (Bader JP, De-Nol Symposium, Sao Paulo, 1986).[4]

How, asks Dr Wormsley, should the data summarised in our leading article influence prescribing? I suggest that it is logical to use tripotassium di-citrato bismuthate for the initial treatment of newly diagnosed duodenal ulcer. Until more information is available I would adopt a conservative approach to retreatment, but even if two four to eight week courses of tripotassium di-citrato bismuthate a year were used the trials analysed in the leading article suggest that about 60% of patients could be kept under control.

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1 Axon ATR. Potential hazards of hypochlorhydria in the treatment of peptic ulcer. *Scand J Gastroenterol* 1986;**21**(suppl 122):17-21.
2 Lechat P, Kisch R. Les encéphalopathies bismuthiques: réévaluation du risque. *Gastroenterol Clin Biol* 1986;**10**:562-9.
3 Hillemand P, Pallière M, Laquais B, Bouvet P. Traitement bismuthique et bismuthémie. *Sem Hôp Paris* 1977;53:1663-9.
4 Lee SP. Studies on the absorption and excretion of tripotassium dicitrato bismuthate in man. *Res Commun Pathol Pharmacol* 1981;**34**:359-64.

SIR,—Clearly, the H_2 antagonists are of proved efficacy both in relieving the symptoms of ulcers and in the acute healing of duodenal ulcers. Drs J Paul Miller and E Brian Faragher (1 November, p 1117) point out that there is accumulating evidence to suggest that ulcers may relapse at a faster rate after initial treatment with an H_2 antagonist than with agents such as tripotassium di-citrato bismuthate. However, neither true natural healing rates nor subsequent relapse rates for duodenal ulcer are accurately known. Most acute and maintenance trials comparing H_2 antagonists or other drugs with placebo have allowed access to antacids or have used antacids as placebo. In addition, when the nature of the placebo was not stated we cannot be certain that it had no acid buffering capacity or could not adhere to an ulcer base, thereby giving some protection.

To obtain accurate information on natural rates of healing and relapse of duodenal ulcer it would be necessary to treat a group of symptomatic patients not with placebo but with nothing. Through a placebo effect, and for the reasons stated above, a