Letters

Obstructive sleep apnoea

False impression of objectivity may deny patients affordable treatment

EDITOR—In their review of the clinical impact of obstructive sleep apnoea and the utility of treatment with nasal continuous positive airways pressure John Wright and colleagues make some important points but give a false impression of objectivity.[1]

Their criteria for excluding abstracts and letters are vague, and the predetermined validity criteria for papers were not well defined—disagreements between the two assessors had to be resolved by a third person. There is evidence of bias, particularly in the discussion on mortality. Two studies in which the design would be unlikely to show any effect are highlighted as showing no significant association between obstructive sleep apnoea and premature death[2 3]; another in which the apnoea index was a predictor of excess mortality[4] is only briefly mentioned and is qualified by the negative statements that the duration of apnoea was not a predictor of mortality and that the excess deaths were not due to heart or lung causes. The important point that the apnoea index was a predictor of premature death was not discussed.

The concept that obstructive sleep apnoea varies from being normal to a life threatening condition is unacknowledged. Results of studies in which most of the patients had only mild disease were used to suggest that there is no link between obstructive sleep apnoea and medical problems. Similarly the authors seem unaware of current medical practice when they state that continuous positive airways pressure is the recommended initial treatment for obstructive sleep apnoea; simple measures such as weight loss are usually tried first.

We are also concerned by the accuracy of the review. There are three errors in the description of our study on nasal continuous positive airways pressure and obstructive sleep apnoea.[5] In table 4 of John Wright and colleagues' paper[1] the desaturation index for patients with mild obstructive sleep apnoea should be 8, not 38; disruptive daytime sleepiness was an indication for starting treatment with continuous positive airways pressure; and "no change in ... symptoms" should read "no new unrelated symptomatic condition developed." These errors completely change the interpretation of our results and raise questions about the accuracy of statements about the other papers quoted.

The impression of objectivity and accuracy and of a scientific approach in this review is illusory. The underlying assumption that clinicians are widely using nasal continuous positive airways pressure in patients without important symptoms is unjustified. It would be unfortunate if this review led to patients being denied a cheap and effective treatment that could prevent them from remaining excessively sleepy for the rest of their lives and running an increased risk of premature death.

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1 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997;314:851-60. (22 March.)
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Superficial analysis ignores evidence on efficacy of treatment

EDITOR—The conclusions of John Wright and colleagues have the potential to jeopardise public health as well as patients' care; their systematic review lacks the necessary depth and understanding of the issues.[1] The authors note that sleep apnoea is currently viewed as a public health concern because it is prevalent and thought to be associated with morbidity and mortality. The collective evidence from the studies included in the review supports this view; the authors' conclusions that evidence for the health effects of sleep apnoea is "weak or contradictory" and that "the relevance of sleep apnoea to public health has been exaggerated" are disturbing.

The authors seem to have misinterpreted the findings of some studies. In their assessment of nine studies of hypertension judged to be methodologically adequate, the authors dismiss seven studies that show an independent association between sleep apnoea and hypertension. The authors choose to base their conclusion solely on the two studies that found no association. The studies that found an association were rejected because associations were found only for blood pressure measured in the morning, or because of failure to control for use of antihypertensive drugs, smoking, or use of alcohol. Acute spikes in blood pressure are known to follow episodes of apnoea and hypopnoea; therefore, it is not unreasonable to expect a stronger effect in the morning. If the effect on blood pressure later in the day is less, the small sample sizes of these studies may have precluded detection. Not controlling for antihypertensive drugs would only serve to reduce a true association. Smoking and alcohol use are unlikely to be strong enough risk factors to cause significant confounding.

Wright and colleagues' review of evidence on treatment with continuous positive airways pressure is also unbalanced. While we support the call for a large randomised clinical trial—the next logical step in this field—there is already evidence for the efficacy of continuous positive airways pressure as evaluated by short term neurobehavioural measures and quality of life assessments. We are concerned that the superficial

Advice to authors

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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, whether typed or sent by email, should give each author's current appointment and full address. Letters sent by email should give a telephone and fax number when possible. We encourage you to declare any conflict of interest. Please send 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.

analysis and conclusions of Wright and colleagues will lead to many patients being denied access to this treatment, which is associated with minimal risks.

Wright and colleagues should be alerted that well designed longitudinal studies on sleep apnoea are under way. We hope that the authors will conduct a more informed review of forthcoming reports.

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Evidence for efficacy of continuous positive airways pressure is compelling

EDITOR—The review by John Wright and colleagues of the complications of obstructive sleep apnoea,[1] a reincarnation of a previous publication,[2] concluded that the relation between obstructive sleep apnoea and hypertension, coronary heart disease, stroke, and premature death are poorly established; this conclusion has been stated many times by other authors, including us.[3] What was new was their inference that the treatment of obstructive sleep apnoea with continuous positive airways pressure is difficult to justify because much of the published evidence is poor or inconclusive. This is wrong since it fails to appreciate that patients are treated for disabling daytime somnolence and not for the risk of cardiovascular disease or premature death. Weak data on cardiovascular aspects are largely irrelevant to the assessment of treatment for this disorder.

How could Wright and colleagues have wandered so far from the mark? We suspect that their error resulted from the simple mistake of reviewing studies and assuming that because most revolve around the cardiovascular-mortality debate, this must be the most important area to consider. This would be a natural mistake for those with no experience of the disease and its management, who thus have no idea that it is mainly hypersomnolence which disturbs patients. There is considerable published work on the cardiovascular and mortality aspects of this disease precisely because this is a highly contentious subject. There are few randomised controlled data on the efficacy of continuous positive airways pressure for overwhelming somnolence because the therapeutic response is so compelling in case reports. Those of us who treat these patients have seen the predicted improvements when patients woken from sleep over 300 times a night for years finally regain normal sleep patterns with continuous positive airways pressure. Perhaps naively we had never expected anyone to question this; neither had we expected the opinions of people with no clinical experience of a complex disease to be taken seriously.

Until there is a fully informed view that includes the skill and experience of those who understand the disease, it would be wrong (and negligent) to base purchasing decisions on this incomplete assessment. An evidence based approach is crucial to clinical medicine and sensible purchasing decisions; it should not be brought into disrepute by being used in an unbalanced way.[4 5]

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1 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997;314:851-60. (22 March.)
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Review was misleading and may deny cost effective treatment to patients

EDITOR—John Wright and colleagues' review of obstructive sleep apnoea[1] and the accompanying comments in Editor's choice[2] and This week in the BMJ[3] have serious adverse implications for many thousands of patients with a severely disabling condition. The review concentrates on the putative association with cardiovascular morbidity and mortality and on treatment with nasal continuous positive airways pressure. The unfortunate juxtaposition of these two topics will mislead readers into assuming that treatment with continuous positive airways pressure is aimed at preventing such complications.

The authors fail to explain that treatment with continuous positive airways pressure is given primarily for relief of disabling daytime sleepiness. We agree that the evidence for a causal relation with vascular disease is tenuous. Unfortunately, however, Wright and colleagues equate morbidity with cardiovascular morbidity and fail to acknowledge the profound morbidity associated with severe sleepiness. The resulting impression is unduly negative, and casual statements such as: "This may not be a disease after all" [2] or not "a separate disease entity"[1] (whatever that means) are potentially highly damaging. Obstructive sleep apnoea cannot be dismissed as merely a manifestation of obesity, as many patients with serious symptoms are not overweight. Because of this mistaken assertion the authors suggest that greater emphasis should be put on weight reduction than on treatment with continuous positive airways pressure. However, there is much less evidence for the effectiveness of dietary treatment than there is for continuous positive airways pressure. Even in obese patients with obstructive sleep apnoea it is inappropriate to deny immediate, inexpensive treatment with continuous positive airways pressure while awaiting an outcome that is rarely achieved.[4]

Wright and colleagues emphasise the need for further placebo controlled studies of continuous positive airways pressure, but the choice of an appropriate placebo is less clear than they assume. Use of a subtherapeutic pressure shows only whether pressure itself has beneficial effects. This approach is not relevant to everyday practice, where the appropriate comparison is between the status quo (or an alternative intervention) and any beneficial effect of continuous positive airways pressure, offset by the inconvenience and discomfort of the associated paraphernalia. However many controlled studies are performed, this decision will inevitably remain a matter of trial and error in individual patients.

The investigation and management of patients with obstructive sleep apnoea in the United Kingdom lags noticeably behind several other countries, including North America, France, Germany, and Australia. We are extremely concerned that the negative attitudes expressed in the *BMJ* will be seized on by NHS purchasers as a reason not to fund effective and inexpensive treatment for a large number of disabled patients.

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1 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997;314:851-60. (22 March.)
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Treatment prevents road accidents, injury, and death caused by daytime sleepiness

EDITOR—In stating that the results of their meta-analysis "do not ... provide sufficiently robust evidence for the effectiveness of continuous positive airways pressure," John Wright and colleagues ignore their own conclusion that sleep apnoea causes sleepiness and possibly road accidents, and thereby injury and death.[1] They also reach the opposite conclusion to that reached by other reports, including one from the Royal College of Physicians[2] and one from the Australian National Health and Medical Research Council and the New Zealand Ministry of Health.[3]

Two randomised controlled trials, one published since Wright and colleagues' analysis was completed, found that patients benefited from continuous positive airways pressure.[4 5] Neither the Royal College of Physicians nor the Australian National Health and Medical Research Council finds the authors' criticisms of the randomised controlled trial by Engleman et al convincing. Indeed, the Australian National Health and Medical Research Council, which

included not only specialists in sleep medicine but other clinicians on their steering committee, found that this study produced "the most compelling evidence of the impact of [continuous positive airways pressure] and that there were no major methodological threats to its validity."[3]

The danger of Wright and colleagues' study is that purchasers of health care within the NHS will give credence to it and cite it as a reason for not providing the appropriate services. To deny this treatment to patients would fly in the face of evidence presented in other reviews and lead to an increase in otherwise avoidable road accidents.

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1 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997;314:851-60. (22 March.)
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Some criticisms of studies are unfounded

EDITOR—At the Scottish National Sleep Laboratory we strongly agree with John Wright and colleagues that further research is required to clarify whether sleep apnoea causes vascular events,[1] and we look forward to contributing to these studies. However, we are disappointed that they are not prepared to support the treatment of sleep apnoea, which, at least in Edinburgh, is aimed at improving symptoms, quality of life, objective sleepiness, and daytime performance. We showed that all of these improved with continuous positive airways pressure[2] in the "one out of 45 studies of continuous positive airways pressure [that was] a truly randomised controlled trial." [1]

We do not believe that the criticism that our study "had important weaknesses" is justified. We are criticised for using an oral placebo instead of a sham continuous positive airways pressure machine. We did this for ethical and scientific reasons as continuous positive airways pressure at subtherapeutic pressure may worsen hypoxaemia during sleep; patients could differentiate between lower sham and higher effective pressure so unblinding the study; and wearing a placebo mask would impair sleep thus biasing in favour of active treatment. Furthermore, machine mystique—the idea that a physical device might have more of an effect than an oral placebo—would be unlikely to influence the objective variables measured more than our actively advocated placebo.

We are criticised for the lack of a washout period, but we did not take any measurements until 28 days after crossover and the benefits of continuous positive airways pressure wear off within one day.[3] We tested for potential carryover by examining order effects using analysis of variance; we accept that between subject effects have lower power than within subject effects, but only the one variable indicated showed a significant ($P < 0.05$) order effect.[2] Critically, we found significant benefits from continuous positive airways pressure while any carryover effect would bias against such findings.

Also, Wright and colleagues omit to indicate that we found significant improvements compared with the placebo in four measures of cognitive function, including intelligence quotient (IQ).

The Australian National Health and Medical Research Council conducted a similarly detailed review and concluded that there was evidence from a randomised controlled trial (level II evidence) and from meta-analysis of other studies (level III evidence) that continuous positive airways pressure was effective and recommended treatment with it for sleepiness and impaired daytime function.[4] This was also the conclusion of the Scottish needs assessment programme.[5] All three reviews [1 4 5] conclude that more evidence is needed about vascular events.

Wright and colleagues' review seems excessively negative about the merits of continuous positive airways pressure for sleepiness and cognitive impairment and this negative conclusion largely centres on their criticism of our study. In contrast, the Australian investigation, while also concerned about the use of an oral placebo, concluded that there were "no major methodological threats to the validity" of our study.[4]

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1 Wright J, Johns R, Watt I, Melville A, Sheldon T. Health effects of obstructive sleep apnoea and the effectiveness of continuous positive airways pressure: a systematic review of the research evidence. *BMJ* 1997;314:851-60. (22 March.)
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Authors' reply

EDITOR—The variety of views expressed by the correspondents reflects the uncertainty about sleep apnoea. The common claim of associations between sleep apnoea and premature death and vascular morbidity[1-3] is reiterated by John Shneerson and Ian Smith. Yet J R Stradling and R J O Davies and G J Gibson and K Prowse agree with us that the evidence is weak. We believe that most patients would be reassured by our conclusion that claims about associations with disability and death are unfounded or premature.

Another example of the uncertainty about sleep apnoea concerns the role of weight reduction. Shneerson and Smith suggest that weight loss is the first line of treatment, yet Gibson and Prowse believe that this is inappropriate and that patients should begin treatment with continuous positive airways pressure straight away. We agree that evidence of the effectiveness of weight reduction on sleep apnoea is lacking, but this probably reflects a lack of interest in this approach rather than a lack of efficacy. The strong association between sleep apnoea and obesity suggests that sleep apnoea may be a symptom of obesity. Surely it is logical to tackle the cause rather than the symptom, particularly in view of the other health benefits derived from weight loss. A recent review has indicated that weight loss interventions can be effective, but it highlights the need for a determined multidisciplinary approach.[4]

Shneerson and Smith correctly point out our typographical error, but we fail to see how the interpretation of their study changes. Our approach in undertaking a systematic review, far from being illusory, is to ensure an objective and scientific review of the evidence. All data from relevant studies are shown in tables so readers can derive their own conclusions. This is an advance on the sort of papers written by enthusiasts who selectively quote studies which support their view and ignore methodological quality.

The accusation that we are suggesting that there is no justification for treatment with continuous positive airways pressure is unfounded. We stated that there can be large benefits from treatment, but that these seem to occur predominantly in patients with very severe sleep apnoea. Clinicians, and their professional organisations, surely have the responsibility to pursue a research agenda to determine in which patients treatment is worth while and cost effective. To suggest, as do Stradling and Davies, that a health service is developed for 2-4% of the middle aged population on the basis of case reports is simply not acceptable.

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1 Phillipson EA. Sleep apnoea—a major public health problem. *N Engl J Med* 1993;328:1271-3.
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Hazards of running a marathon

41-Fold increase in creatine kinase has been reported

EDITOR—The recent grand round from Hammersmith Hospital pointed out that, 24 hours after a marathon run, creatine kinase activity may be raised in the absence of myocardial infarction.[1] The author recorded a total creatine kinase activity of 1800 IU/l 24 hours after a marathon, causing the registrar in chemical pathology who was on duty to think temporarily that the 61 year old runner might have had a myocardial infarction.

In 1984 I described my own experience of measuring multiple variables during a marathon run.[2] The creatine kinase activity before the race was 83 IU/l, and at 8, 16, and 24 km it was 111, 133, and 168 IU/l respectively. At the end of the run the activity had risen to 480 IU/l, and the next day it was 3410 IU/l. Two days later the activity was 1965 IU/l, seven days later it was 136 IU/l, and it had fallen to a normal 63 IU/l by the 28th day. At the time I was 32 years old; my electrocardiogram before and after the race was normal, and at no time did I experience any chest pain.

One other finding was that the concentration of most plasma non-essential amino acids fell towards the end of the race, but no appreciable changes were observed in the concentration of any of the essential amino acids except lysine. My colleagues and I speculated that at times of metabolic need the body has a preservation mechanism for essential amino acids. It is not clear why lysine was an exception to this rule.

The article in the *BMJ* referred to work by Siegel et al showing a rise of creatine kinase MB activity by a factor of 15.[3] My own activity of total creatine kinase rose to 41 times the starting value. I agree entirely with the conclusion that this is a transient rhabdomyolysis of skeletal muscle.

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1 Thompson GR. Hazards of running a marathon. *BMJ* 1997;314:1023-5. (5 April.)
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Troponin-T concentrations should be measured

EDITOR—A recent grand round from Hammersmith Hospital highlights the hazards of marathon running.[1] The possibility of raised creatine kinase MB activity without myocardial infarction after prolonged physical endurance is well documented. G R Thompson also states[1] that the absence of a rise in cardiac troponin-I or C reactive protein concentration in one study argues against a cardiac origin of creatine kinase MB.[2] Troponin-T concentrations have, however, been measured in five athletes participating in an ultramarathon endurance race, none of whom clinically had infarction. All five subjects had raised creatine kinase, creatine kinase MB, and cardiac troponin-T values in samples obtained after the run; values in samples obtained before the run were within normal limits.[3] The two participants who successfully completed the 100 mile (160 km) endurance run were found to have the highest troponin-T concentrations. Cardiac troponins should be measured in athletes with raised creatine kinase MB activity after strenuous exertion, as such measurement is a more sensitive and specific assay to confirm or exclude myocardial injury. Why prolonged strenuous exercise should induce myocardial injury remains unclear.

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1 Thompson GR. Hazards of running a marathon. *BMJ* 1997;314:1023-5. (5 April.)
2 Cummins P, Young A, Auckland ML, Michie CA, Stone PC, Shepstone BJ. Comparison of serum cardiac specific troponin-I with creatine kinase, creatine kinase MB isoenzyme, tropomyosin, myoglobin and C-reactive protein release in marathon runners: cardiac or skeletal muscle trauma? *Eur J Clin Invest* 1987;17:317-24.
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Unexpected findings of study of selegiline have not been treated with caution its authors advised

EDITOR—In 1995 the *BMJ* published the results of a study by the Parkinson's Disease Research Group of the United Kingdom comparing the use of levodopa and a peripheral decarboxylase inhibitor either with or without selegiline.[1] An unexpected finding was an increase in mortality in the group receiving selegiline. The authors stated at that time that "the difference in mortality should be treated with caution." An editorial in the same issue also suggested that the findings provided "strong evidence against selegiline having a neuroprotective action."[2] The articles generated considerable correspondence, and a reply from the authors emphasised that "a causal relation between long term selegiline (10 mg/day) and the increased mortality...had not been established."[3] The debate continues.[4 5]

Once a year the Parkinson's Disease Society of the United Kingdom holds an open day at the Neurodegenerative Diseases Research Centre, King's College, London. The meeting is attended by patients with Parkinson's disease from across Britain and provides an opportunity to obtain an overview of prescribing practice in Britain. This year patients were asked if they had been taking selegiline in November 1995 (before publication of the British paper) and if they were still taking it at the time of questioning (10 May 1997). Forty eight patients responded.

In November 1995, 34 of the respondents were taking selegiline (table). By May 1997 two thirds of these had stopped taking it. Among the 11 patients who continued to take it, an unsuccessful attempt at withdrawal had been made in three, making a total of 37 patients in whom withdrawal of selegiline had been attempted.

Use of selegiline in November 1995 and May 1997 by 48 patients

	May 1997	
Nov 1995	**Yes**	**No**
Yes	11	23
No	0	14

This is a small, well informed and selected group which may not be representative of the population with Parkinson's disease as a whole. The fact that an attempt to stop treatment with selegiline has been made in a substantial proportion of patients with Parkinson's disease indicates a major shift in prescribing practice in Britain. As predicted, the unexpected findings of the study by the Parkinson's Disease Research Group of the United Kingdom have not, at least in Britain, been treated with the caution that its authors advised.[1 3] The results of further trials of selegiline and updates on the ongoing trial by the Parkinson's Disease Research Group of the United Kingdom and the United States Parkinson's Study Group's deprenyl and tocopherol antioxidative therapy of parkinsonism trial are eagerly awaited. In view of the continuing controversy, surely the death of selegiline in Britain is premature.

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1 Lees AJ on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *BMJ* 1995;311:1602-7.
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Drug treatment for benign prostatic hyperplasia

Health authorities must audit use of finasteride

EDITOR—Andrew Farmer and Jeremy Noble are right to draw attention to the results of a recent trial which showed that finasteride, a 5α-reductase inhibitor, was little better than placebo in a group of men with moderate symptoms of benign prostatic hypertrophy.[1 2] The mean prostatic volumes in this trial were in the range 36.2-38.4 cm^3, which

is lower than the volume in other, more positive, trials that have assessed the efficacy of finasteride.[3]

Health authorities have a duty to ensure that prescribing is both clinically and cost effective.[4] One can deduce, therefore, that the use of finasteride in men with moderate symptoms of benign prostatic hyperplasia and moderately enlarged prostates is neither. Moreover, expenditure on finasteride by health authorities is considerable. We have examined expenditure on and prescribing rates for finasteride in our district over the past two years, using the health authority electronic prescribing analysis and cost system.

We found that 8469 items were prescribed at a total cost of £289 305. Quarterly costs have increased from just over £28 217 to £38 485, and practice prescribing rates per quarter (ended September 1996) varied considerably, from £77.82 per 1000 ASTRO-PUs (age, sex, and temporary resident originated prescribing units) to £1.77 per 1000 ASTRO-PUs. Some practices have never prescribed this treatment. It is right that the appropriateness of the use of medicines should be monitored, and health authorities would do well to audit the use of finasteride.

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Several trials have shown benefit of finasteride

Editor—The editorial by Andrew Farmer and Jeremy Noble overlooks recent evidence relating to the role of finasteride in the management of benign prostatic hyperplasia.[1] The Veterans Affairs' study did imply that finasteride had little benefit over placebo except in larger glands,[2] but the distribution of prostatic volume in that study was similar to that in the community.[3]

A recent meta-analysis of randomised trials involving 2601 men identified prostatic volume as a strong predictor of clinical outcome of finasteride treatment, showing a modest but significant improvement in peak flow rates and symptom scores in men with glands >40 cm^3.[4] A volume of 40 cm^3 is not substantial enlargement in my view; over one third of men aged over 60 with benign prostatic hyperplasia in the community have glands larger than this.[3]

Another study, a post hoc analysis of 4222 men, showed a 57% reduction in episodes of acute retention and a 34% decrease in rates of surgical intervention in patients given finasteride compared with patients given placebo.[5] This implies that finasteride has considerable potential to influence both the natural course of benign prostatic hyperplasia and the associated morbidity, contrary to the editorial's conclusions. Furthermore, I am not aware of any evidence suggesting that finasteride masks prostate cancer because of the 50% reduction in concentrations of prostate specific antigen that occurs after treatment. Doctors merely multiply the concentration by two to interpret the laboratory result in patients taking finasteride.

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To interpret PSA concentrations in patients taking finasteride, multiply them by two

Editor—In their editorial on drug treatment for benign prostatic hyperplasia Andrew Farmer and Jeremy Noble mention concerns about the fact that the concentration of prostate specific antigen is halved in patients taking finasteride.[1] Every clinician who manages patients taking finasteride should be aware of this important point. Guess et al found that in men with benign prostatic hyperplasia the normal reference range of serum prostate specific antigen concentration in those with no evidence of prostate cancer who were treated with finasteride for six months or longer was half that in untreated men.[2] Continuing finasteride treatment beyond six months did not cause any further reduction in the antigen concentration. They therefore recommended that, to interpret serum prostate specific antigen concentrations in men with benign prostatic hyperplasia treated with finasteride for six months or longer, the concentration should be multiplied by two and compared with either age independent or age specific upper limits of normal concentrations in untreated men with the condition.

It is a good clinical practice to measure the prostate specific antigen concentration before the start of treatment with finasteride and then to obtain a repeat measurement after six months to define the new baseline concentration for the patient. While an increase in the concentration above the baseline value in a patient taking finasteride raises the suspicion of carcinoma of the prostate, poor compliance is one of the reasons for raised concentrations. If compliance is in question, estimation of serum dihydrotestosterone concentrations is helpful as they are low in patients taking finasteride regularly.

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Criticism of prophylaxis of gastrointestinal bleeding with H_2 receptor antagonists is wrong

Editor—The short report by D L A Wyncoll and colleagues is provocatively titled "H_2 blockers in the intensive care unit: ignoring the evidence?"[1] The authors state that a recent meta-analysis by Cook et al has "shown that sucralfate is associated with a lower incidence of pneumonia and mortality than H_2 receptor antagonists."[2] They infer that patients referred to their unit who continue to receive H_2 receptor antagonists are receiving suboptimal treatment.

The paper by Cook et al sought to resolve the results of previous meta-analyses on this subject that had discordant findings. The authors were a combination of the authors of several previous analyses.[3-5] In their abstract they state that "sucralfate may be as effective in reducing bleeding as gastric pH-altering drugs and is associated with lower rates of pneumonia and mortality." When one reads the paper more critically several points emerge.

- "Histamine receptor antagonists (and antacids) are associated with a trend toward lower clinically important bleeding rates than sucralfate is" (odds ratio for sucralfate *v* H_2 blockers 1.28 (95% confidence interval 0.27 to 6.11)).
- "A trend toward a lower incidence of pneumonia was identified when sucralfate was compared with H_2 receptor antagonists" (odds ratio for sucralfate *v* H_2 blockers 0.78 (0.6 to 1.01)).
- "Compared with ... H_2 receptor antagonists sucralfate was associated with reduced mortality" (odds ratio for sucralfate *v* H_2 blockers 0.83 (0.62 to 1.09)).
- Cook et al interpret odds ratios as follows: an odds ratio of <0.8 or >1.2 represents a "trend" and one of <0.7 or >1.3 represents a "strong trend" (provided, in both cases, that the confidence intervals are not too wide). In each of the results quoted above the confidence interval for the odds ratio included 1.0, albeit only marginally in one case. In their comment Cook et al report both of these findings (reduced pneumonia and reduced mortality with sucralfate) as trends. If appropriate rigour is applied to interpreting the results these trends do not represent a significant difference between sucralfate and H_2 receptor antagonists. This is despite the inclusion in the meta-analysis of studies of over 7000

patients. Findings in Cook et al's paper that do reach significance include the finding that use of H_2 receptor antagonists decreases overt and clinically important gastrointestinal bleeding.

- While the possibility that sucralfate may be as effective as H_2 receptor antagonists and associated with lower morbidity and mortality is not excluded, the quoted study does not provide adequate evidence on which to criticise those who continue to use H_2 receptor antagonists as prophylaxis against gastrointestinal bleeding in critically ill patients.

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Treatment of pregnant women with recurrent miscarriage associated with phospholipid antibodies

General prognosis is favourable in untreated women

EDITOR—R Rai and colleagues claim that rates of live births are increased in women with recurrent miscarriage who are positive for phospholipid antibodies when they are treated with low dose aspirin alone and are further improved when heparin is added.[1] They state that the fetal loss rate is 90% when no treatment is given, and an editorial claims that several non-randomised studies suggest that low dose aspirin is an effective treatment for these women.[2]

I disagree with these claims. A series of prospective studies has indicated that the fetal loss rate in untreated women with recurrent miscarriage and cardiolipin antibodies is considerably less than 90%. My group conducted a prospective controlled trial of allogeneic lymphocyte immunisation versus infusion of autologous leucocytes in women with recurrent miscarriage, irrespective of their cardiolipin status.[3] All women were tested for cardiolipin antibodies twice: at their first visit (when they were not pregnant) and again as soon as they achieved pregnancy—in almost all cases this was at least two months after the first test. Investigations were done with an enzyme linked immunosorbent assay (ELISA) that fulfils generally accepted recommendations. Cardiolipin values were considered to be raised (>7.0 MPL units or >22.0 GPL units; for definitions see Rai and colleagues' paper) when they exceeded the 95% centile of the measurements in a control group of women of fertile age.

None of the 71 patients participating in the trial received any treatment with aspirin, heparin, or steroids. Nine patients were positive for either IgM or IgG cardiolipin antibodies both at the first visit and in early pregnancy. Five of these (56% (95% confidence interval 21% to 86%)) miscarried, whereas the four others gave birth to live infants (median birth weight 3010 g). Two of these four women had high titres of cardiolipin antibody in both samples (>68 GPL units). One of the women who miscarried had a successful pregnancy a few months later without further treatment. The 57 women who were negative for cardiolipin antibodies both at the first visit and during pregnancy had a miscarriage rate of 33% (21% to 47%) and gave birth to children with a median birth weight of 3435 g (3220 g to 3720 g).

These results, in conjunction with those of other trials,[4 5] support the view that the presence of cardiolipin antibodies in women with recurrent miscarriage may result in a modest increase in the risk of fetal loss. The chance of a successful pregnancy even without anticoagulant treatment, however, is still favourable.

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1 Rai R, Cohen H, Dave M, Regan L. Randomised controlled trial of aspirin and aspirin plus heparin in pregnant women with recurrent miscarriage associated with phospholipid antibodies (or antiphospholipid antibodies). *BMJ* 1997;314:253-7. (25 January.)
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No cytogenetic data were reported

EDITOR—We were concerned by R Rai and colleagues' paper advocating treatment with heparin throughout pregnancy for women with recurrent miscarriage and phospholipid antibodies.[1] Most women in their study had isolated first trimester losses and had previously given birth to live infants at term; the authors do not provide any necropsy or cytogenetic data so that readers can assess the likely relation between pregnancy loss and placental damage from phospholipid antibodies.

Figure 1 in their paper shows that heparin seemed to benefit women only in the first trimester—a form of "embryonic" treatment. Substantial literature suggests, however, that there is no intervillous circulation in the placenta before 11 weeks' gestation because the intact trophoblastic shell is an anatomical barrier to maternal blood.[2] How did the authors expect heparin to prevent early pregnancy loss?

The main mechanism of early pregnancy loss, even for parents with normal chromosomes, is aneuploidy. The authors ignored this fact, and the alleged superiority of heparin is based only on an excess survival of 13 embryos (table 4 in the paper). No cytogenetic data were reported, so readers are unable to assess whether heparin prevented the loss of pregnancies in which the fetus was chromosomally normal. Aneuploidy is associated with an increased nuchal translucency in the first trimester.[3] As the women were scanned frequently in early pregnancy we would be interested in the nuchal data as a surrogate marker of aneuploidy to address this weakness.

A median IgG cardiolipin value of 12.5 GPL suggests that up to 40% of the values were <10 units, the threshold that we normally regard as indicating abnormality in the absence of previous thrombotic events. Remarkably few women required early delivery of their babies, which suggests that few had placental disease. Despite serial umbilical artery Doppler measurements no such data were reported or incorporated into the diagnostic criteria for intrauterine growth retardation.[4] One might therefore conclude that intrauterine growth retardation did not complicate these pregnancies. Lack of systematic examination of the placenta (at any gestation) is a serious omission though not confined to this study,[5] and thus no plausible mechanism can be offered for the proposed benefit of heparin in later pregnancy.

The results of this study could lead to the mistaken notion that recurrent miscarriage can be treated with expensive and time consuming treatment with a potentially harmful drug. Further randomised studies, with cytogenetic analysis of all losses of previable fetuses and histological examination of all delivered placentas, are urgently required so that we can be certain that heparin treatment results in more good than harm.

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During pregnancy, heparin should be stopped during labour and then restarted soon after delivery

EDITOR—R Rai and colleagues show the superiority of aspirin plus heparin compared with aspirin alone in pregnant women

with recurrent miscarriages and phospholipid antibodies.[1] The duration of treatment used in the trial protocol might not, however, be optimal.

Firstly, most miscarriages occurred before 13 weeks' gestation, and the improved prognosis associated with the use of heparin resulted from a reduction in these early miscarriages. As the authors suggest, earlier introduction of heparin—that is, as soon as a pregnancy test gives a positive result instead of at the time that fetal heart activity is detected—might potentially improve the rate of live births.

Secondly, the rationale for stopping treatment at 34 weeks' gestation is questionable, even though the patients in the study had not had thromboembolism previously. Pregnancy is itself a prothrombotic state. Indeed, the risk of venous thromboembolism associated with pregnancy (during the third trimester or post partum) was found to be increased eightfold in women with various forms of anticoagulant factor deficiency compared with family controls without such deficiency.[2] In the series of 70 patients with the phospholipid syndrome reported on by Rosove and Brewer, eight had their first thrombotic event during pregnancy or post partum.[3] Furthermore, we have reported cerebral infarction during the immediate postpartum period eight days after withdrawal of aspirin in a woman with systemic lupus and phospholipid antibodies who had no history of thrombosis.[4] Though no thromboembolic complication was observed after treatment was stopped in Rai and colleagues' study, one woman developed pre-eclampsia at 36 weeks' gestation, two weeks after the withdrawal of aspirin.

As pregnancy in the phospholipid syndrome is a challenge to both mother and baby,[5] we believe that when heparin is used during pregnancy it should be stopped during labour, restarted 12-24 hours after delivery, and continued for several weeks during the puerperium.

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Authors' reply

EDITOR—In contrast to Ole B Christiansen's assertions, most reports have clearly shown that the presence of cardiolipin antibodies confers a significant risk of an adverse outcome of pregnancy among both women with recurrent miscarriage[1] and unselected populations with no history of pregnancy loss.[2] In our prospective study women were followed up from the time that a pregnancy test gave a positive result.[3] There was a 90% fetal loss rate in pregnant women with recurrent miscarriage associated with phospholipid antibodies and/or lupus anticoagulant and/or cardiolipin antibodies. There was a 100% fetal loss rate among those with lupus anticoagulant alone and a 60% loss rate among those with cardiolipin antibodies alone. Importantly, most women with recurrent miscarriage and phospholipid antibodies are positive for lupus anticoagulant alone. Studies reporting a lower miscarriage rate have included only women followed up from the time that they booked for antenatal care at the end of the first trimester, which is after most miscarriages have occurred.

We included in our trial only women in whom tests for phospholipid antibodies gave persistently positive results. Guidelines issued by the Association of Clinical Pathologists recommend that an IgG cardiolipin antibody concentration >5 GPL units and an IgM cardiolipin antibody concentration >3 MPL units should be regarded as being positive.[4] We adhered to these guidelines.

Cytogenetic data on the products of conception from women who miscarried are incomplete because most women attended their local hospital for uterine evacuation after a diagnosis of miscarriage. The fetuses of the four women who had a second trimester miscarriage had a normal karyotype. Cytogenetic data are available on 12 of the fetuses from the 24 first trimester miscarriages. Ten fetuses had a normal karyotype. Among the women treated with aspirin and heparin, cytogenetic analysis showed that the fetuses of six of the eight who miscarried in the first trimester had a normal karyotype. As the patients were randomly allocated to treatment it is reasonable to expect there to have been a similar rate of aneuploidy in the two treatment arms.

We agree with Jean-Charles Piette and colleagues that an argument can be made for continuing heparin until delivery, on the grounds of maternal welfare. Our trial, however, was designed to assess the best treatment for reducing the risk to the fetus in pregnancies complicated by the presence of phospholipid antibodies. As the live birth rate among pregnancies that reached 14 weeks' gestation did not differ between the two treatment arms we are investigating whether heparin treatment can be stopped after this time.

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Casualties of Gulf war were higher than most reports suggest

EDITOR—In his letter discussing why it took so long to investigate the problem of the Gulf war syndrome, Peter Beale states that "casualties [were] mercifully few."[1] He refers, of course, only to casualties among the Allied forces and disregards the 100 000 Iraqi conscripts and an unquantified but probably greater number of civilians who died.[2] I find it worrying that the chief medical adviser to the British Red Cross Society regards the death of more than 200 000 people, whose only crime was to be on the losing side, to be a matter of so little consequence as to be unworthy of mention.

The American linguist and social critic Noam Chomsky has argued cogently that the prime function of the mass media is to create a climate of consensus (or to "manufacture consent," as he describes it) for whatever actions the government of the day deems to be in the national interest.[3] (This is not always successful, as evidenced by the collapse of popular support for the Vietnam war during its later stages.) This strategy was used forcefully both before and during the Gulf war, with little objective discussion of the alternatives to armed intervention or of the overall aims of the war. Great publicity was given, however, to the technology and weaponry, with the clear intention of convincing the public that the conflict could be won with the absolute minimum of "collateral damage"—that is, civilian deaths—to make the action more palatable.

The mendacity of many of these claims was evident within a short time after the end of the war, when it became clear that the collateral damage was, in reality, extensive and compounded by starvation and disease resulting from the collapse of the infrastructure in Iraq. It is regrettable that a medical journal such as the *BMJ* allows itself to publish a letter repeating the official version of the number of casualties.

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