—would have yielded false positive results, so someone with a positive result on screening would have a 1 in 19 chance of developing clinical prostate cancer within three years. The authors do not mention this but instead invoke calculations based on population based data (not from this study) to argue that looking at men aged 60-74 would give the much more impressive specificity quoted in their conclusion.

We must speculate why we are not told how many of the men aged 60-74 who were studied had ≥ 12 times the normal median concentration of prostate specific antigen but did not get prostate cancer. The investigators must know these data, and omitting them severely damages the credibility of the conclusion.

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1 Parkes C, Wald NJ, Murphy P, George L, Watt HC, Kirby R, *et al.* Prospective observational study to assess value of prostate specific antigen as screening test for prostate cancer. *BMJ* 1995;311:1340-3. (18 November.)

Paper gives misleadingly optimistic view

EDITOR,—Fifteen per cent of men aged 55-69 have prostate cancer; tumours are detected in 5% by rectal examination, measurement of prostate specific antigen, and transrectal ultrasonography plus biopsy. Only 1%, however, develop clinical cancer. How did Carol Parkes and colleagues find that measurement of prostate specific antigen is a good predictor?¹

They achieved their results (85% sensitivity, 0.5% false positivity) by using prostate specific antigen concentrations of ≥ 12 multiples of the median and by concentrating on men presenting within three years of blood sampling. Tumours presenting after a short time are advanced and incurable: figure 2 in the paper therefore provides a deceptively optimistic view of the utility of this test. Prostate cancer progresses slowly, and men presenting after more than six years, who are likely to benefit from curative treatment, are missed when high prostate specific antigen concentrations are used for screening (their figure 1). Within six years 45 tumours were detected, of which 18 were predicted by the prostate specific antigen concentration; within 10 years 101 tumours presented, but only 22 were predicted. Thus, of the 56 tumours presenting between six and 10 years, only four (sensitivity 7%) were predicted by a prostate specific antigen concentration ≥ 12 multiples of the median (table III). Data from men presenting beyond 10 years (164 men) are not given; the sensitivity must have been worse. These data do not support the contention that measurement of prostate specific antigen is "good enough to justify a trial of screening": even if it were, screening should not be performed until trials have shown radical treatment to be better than watchful waiting.

Table III shows that the sensitivity for detection of tumours presenting between six and 10 years was 7% (4/56) for > 12 multiples of the median, 16% (9/56) for > 8 multiples of the median, and 27% (15/56) for > 4 multiples of the median; increased sensitivity has the price of an increased number of false positive results. The variance among centres in median control prostate specific antigen concentrations (0.47-0.75 ng/ml) is worrying. Given the retrospective nature of data collection on cancers, tumours must have been missed, and the assumption that all cancers that presented clinically were important is false because some would have been unsuspected cancers detected after transurethral prostatectomy (many of which are low stage).

By concentrating on men with high prostate specific antigen concentrations presenting soon

after testing, the authors have promoted a misleadingly optimistic view of prostate specific antigen testing.

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- 1 Parkes C, Wald NJ, Murphy P, George L, Watt HC, Kirby R, *et al.* Prospective observational study to assess value of prostate specific antigen as screening test for prostate cancer. *BMJ* 1995;311:1340-3. (18 November.)
- 2 Catalona WJ, Richie JP, Ahmann FR, Hudson MA, Scardino PT, Flanigan RC, *et al.* Comparison of digital rectal examination and serum prostate specific antigen in the early detection of prostate cancer: results of a multicentre clinical trial of 6630 men. *J Urol* 1994;151:1283-90.

Trials of treatment are needed before trials of screening

EDITOR,—Considerable uncertainty still exists in the urological community about the importance and the optimal management of localised carcinoma of the prostate. The options are watchful waiting, radiotherapy, and radical prostatectomy. The benefits of radical prostatectomy have not been proved.¹ There is an associated mortality, and complications include impotence and incontinence. Radiotherapy offers no advantage over watchful waiting.² Screening is not benign and is associated with psychological morbidity.³ Is it therefore ethical to instigate a trial of screening, as suggested by Carol Parkes and colleagues,⁴ when the optimal management of this disease is uncertain?

Systematic reviews of the available evidence comparing various modalities of treatment with conservative management have found the data inadequate for valid comparisons.⁵ If the basic tenet of screening is to be fulfilled there must be an effective treatment that can reduce mortality related to the disease. Otherwise the use of screening may merely increase lead and length time bias. Randomised studies comparing the most promising treatment with conservative management are required before a trial of screening is undertaken.

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- 1 Graverson PH, Nielson KT, Gasser TC, Corle DK, Madsen PO. Radical prostatectomy versus expectant treatment in stage I and II prostate cancer. A fifteen year follow up. *Urology* 1990;36:493-8.
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- 4 Parkes C, Wald NJ, Murphy P, George L, Watt HC, Kirby R, *et al.* Prospective observational study to assess value of prostate specific antigen as screening test for prostate cancer. *BMJ* 1995;311:1340-3. (18 November.)
- 5 Middleton RG, Thompson IM, Austenfeld MS, Cooner WH, Correa RJ, Gibbons RP, *et al.* Prostate cancer clinical guidelines: panel summary report on the management of clinically localized prostate cancer. *J Urol* 1995;154:2144-8.

Measurement presents technical difficulties

EDITOR,—In their evaluation of measurement of the prostate specific antigen concentration as a screening test for prostatic cancer Carol Parkes and colleagues advocate the use of values expressed as multiples of the median value in a healthy

population matched for age.¹ Currently, laboratories report actual numerical values for prostate specific antigen.

The authors do not discuss the technical difficulties in measuring the low prostate specific antigen concentrations seen in healthy men, which affect the reliability of median values. The authors used the Tandem-R prostate specific antigen assay (Hybridtech), in which the two lowest standards used for calibration are zero and 2.0 ng/ml. All their median values in normal men were < 2.0 ng/ml and therefore fall in the range of the assay that has greatest imprecision. Variability arises because of counting error and a greater proportional contribution of misclassification errors at low concentrations.

In addition, the use of different standard curve fitting techniques can lead to considerable differences between laboratories. By applying two different curve fits to a single dataset we could alter the apparent prostate specific antigen result from 0.56 to 0.67 ng/ml. Such small apparent differences become important when medians are multiplied by large numbers to produce cut off values (for example, the 12 multiples of the median recommended by Parkes and colleagues as a clinical cut off would, in our example, give values of 6.7 and 8.0 ng/ml, respectively). In addition, prostate specific antigen concentrations were reported to two decimal places, which implies a detection limit of 0.01 ng/ml. Since the manufacturers of the kit quote a detection limit of 0.1 ng/ml and since between batch imprecision of the assay in our hands is $> 3\%$ at values < 1.0 ng/ml, we suggest that it is inappropriate to report results to two significant figures.

The principle that Parkes and colleagues use is currently used in biochemical screening for Down's syndrome with assays of human chorionic gonadotrophin and α fetoprotein. For prostate specific antigen, however, the authors imply characteristics of the assay that do not reflect its actual performance. If the median data are flawed then the advantage of an approach in which concentrations are expressed as multiples of those medians should be questioned.

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Authors' reply

EDITOR,—Paul Warren suggests that we should estimate the predictive value of measurement of prostate specific antigen direct from our data. The predictive value of a positive result depends on the prevalence of the disease. Our population included a high proportion of men under 60 (median age of those with the disease 57), so an estimate of the positive predictive value in our subjects would be lower than one based on older men, in whom the disease is more common. If screening were shown to be effective then measurement of prostate specific antigen would be best offered to men over 60. That is why we based our estimates on men aged 60-74, applying the detection and false positive rates to the prevalence of the disease in this age group.

D E Neal and F C Hamdy suggest that the prediction of cancer that would present clinically over the next three years is of no value. There is no evidence of this, and that is what a trial of screening and treatment needs to determine. The result should not be prejudged. An important and surprising observation was that, of 22 cancers that