the risk of carcinoma of the endometrium rather than of "uterine neoplasia" developing in patients given bromocriptine.

Cancer of the body of the uterus commonly occurs in postmenopausal women and it is in these subjects that the carcinogenic risk of bromocriptine might be expected first. Though the reliability of the diagnosis of endometrial status by histological examination of tissue obtained with the Vabra curette is unquestionable, histological assessment was performed in only one postmenopausal woman given bromocriptine. A diagnosis by cytological examination of endometrial aspirates was made in four additional cases. The accuracy of diagnosis from the cytology of aspirates obtained with the Vabra curette is, however, presently unknown. Cervical cytology is not a reliable method of assessing endometrial status.¹ Thus the status of the endometrium in only five postmenopausal subjects given bromocriptine has been reported and its accuracy in four of these cases is uncertain.

In general, prolonged exposure to chemical agents is required before their carcinogenic potential can be evaluated. For instance, in the case of oestrogen and endometrial cancer the risk is clearly related to the duration of therapy and it is hardly increased in the first five years of treatment.² In the report of bromocriptine a total of only six patients had received the drug for more than four years, though it is not in fact clear whether these patients were in the group in which endometrial tissue was available for histological assessment. Thus the number of relevant cases upon which the study was based is hardly enough to justify the reassurance implicit in the paper's title, "Absence of uterine neoplasia in patients on bromocriptine."

Finally, we are unable to understand the suggestion advanced in the paper and the accompanying leading article (p 846) that "bromocriptine may actually protect hyperprolactinaemic women with menstrual abnormalities against cancer of the endometrium." We know of no evidence that women with hyperprolactinaemia are specially at risk from endometrial cancer and indeed, since those with amenorrhoea are characteristically oestrogen-deficient,³ an increased risk of endometrial cancer in these patients seems quite improbable.

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¹ Anderson, D G, *et al*, *American Journal of Obstetrics and Gynecology*, 1976, **125**, 356.

² Gray, L A, Christopherson, W M, and Hoover, R N, *Obstetrics and Gynecology*, 1977, **49**, 385.

³ Jacobs, H S, *et al*, *Clinical Endocrinology*, 1976, **5**, 439.

* * We sent copies of these two letters to Professor Besser, whose reply is printed below.—ED, *BMJ*.

SIR,—Dr Rose has quoted us out of context. Our tentative suggestion that the resumption of normal ovulatory menstruation induced by bromocriptine in otherwise anovulatory, often amenorrhoeic women may protect them from uterine malignancy is not inferred from the results of the examination of our patients. As indicated in the discussion, this suggestion refers to the reversal of the apparent increased risk of uterine malignancy in women with anovular, irregular, or absent periods, which can be reduced by induction of regular

menstruation according to the references we quoted.^{1,2} Despite these considerations, and although we found no evidence of premalignant or malignant change in the patients studied, we felt that the observation of malignancy in rats could not be ignored. In order to confirm or refute our provisional conclusion that this valuable drug does not carry any significant risk we therefore advised that "patients on long-term treatment should undergo gynaecological assessment... every year during treatment until enough data are accumulated." Any other advice would seem irresponsible.

We agree with Dr Jacobs and Mr Hutton that there is no substitute for a prolonged follow-up study to assess the human carcinogenicity of a newly introduced compound such as bromocriptine. Unfortunately, however, this drug has only been in regular clinical use in hyperprolactinaemic states for six years.³ When presented with the animal data, however, we were concerned, for ethical considerations, to screen as many of our female patients on bromocriptine as possible for evidence of uterine malignancy and therefore assessed the 108 currently under our supervision. Ten were pregnant and 10 had had hysterectomies. Of the remaining 88, it is true that only six patients had received treatment for between four and six years, but this is the longest time any patient could have taken this drug, as it was unavailable earlier. Endometrial histology was normal in each of these six patients. We were relieved to discover no evidence of endometrial or cervical malignancy and no premalignant changes in any menopausal or premenopausal patient irrespective of dose or duration of therapy. Endometrial cytological or histological tissue was obtainable from only five of 11 postmenopausal patients and we feel that the absence of curettage tissue in a further three, despite careful examination, would suggest that it is unlikely that endometrial hyperplasia or neoplasia was present. It was not possible to insert the curette in three patients (one each virgo intacta, cervical stenosis, and anxiety). Cytological and histological assessment was available respectively in 74 and 61 of 77 premenopausal patients and was similarly reassuring. We hope that Dr Jacobs and Mr Hutton are also reassured that the use of this compound, found to produce uterine malignancy in the rat, was not associated with any evidence of endometrial hyperplasia or neoplasia in our large group of bromocriptine-treated patients, treated albeit only for up to six years, and that they are pleased as well that the cervical cytology was normal. We did not claim any endocrine basis for cervical cancer but merely reported our observations. We hope that they and others will find similar results. Since we are still dealing with a new compound we felt it important to stress that regular surveillance of the patients on long-term therapy is advisable; we are pleased that Dr Jacobs and Mr Hutton agree that more prolonged follow-up studies are needed.

The original studies of bromocriptine treatment in the rat are not our own and clearly we are not at liberty to publish the data. Doubtless they will be available in due course and we understand that they have been presented to the appropriate drug regulatory authorities worldwide.

Our suggestion that bromocriptine-induced resumption of ovulatory menstruation in women with amenorrhoea or dysfunctional uterine bleeding might protect against endometrial cancer was not based on data relating

to prolactin levels, since there are none. We do not find oestrogen deficiency characteristic of hyperprolactinaemic states and indeed would not interpret the published evidence as being in favour of this view. As to the title of our paper, it was simply factual—evidence for uterine neoplasia (endometrial or cervical) in our patients treated with bromocriptine was absent.

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¹ Vellios, F, in *Genital and Mammary Pathology Decennial 1966-75*, ed S C Sommers, p 55. New York, Appleton-Century-Crofts, 1975.

² Nordqvist, S R B, in *Genital and Mammary Pathology Decennial 1966-75*, ed S C Sommers, p 85. New York, Appleton-Century-Crofts, 1975.

³ Besser, G M, *et al*, *British Medical Journal*, 1972, **3**, 669.

Eating bracken shoots

SIR,—Our attention has been drawn to your expert's answer in Any Questions? (10 September, p 693). Bracken contains a number of toxic chemicals and is, moreover, carcinogenic in all species of animals tested so far, with the possible exception of the pig. It produces a wide variety of tumours, including highly malignant intestinal adenocarcinoma in the rat and quail and gastric squamous carcinoma in the mouse.¹⁻³ In Japan, where the incidence of human gastric carcinoma is high, bracken is frequently eaten, and normal cooking does not completely eliminate its carcinogenicity in animals.¹ It is possible also that milk, dairy products, and water may be contaminated by the chemicals in bracken.³ For these and other reasons it seems wise to refrain from eating bracken in any form.

Our work is supported by the Cancer Research Campaign.

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¹ Evans, I A, *Cancer Research*, 1968, **28**, 2252.

² Evans, I A, *Botanical Journal of the Linnean Society*, 1976, **73**, 105.

³ Evans, I A, in *Chemical Carcinogens*, ed E Searle, American Chemical Society Monograph No 173, 1976.

⁴ Hirono, I, *et al*, *Journal of the National Cancer Institute*, 1970, **45**, 179.

⁵ Evans, I A, Jones, R S, and Mainwaring-Burton, R, *Nature*, 1972, **237**, 107.

Surgeons and money

SIR,—As a co-author of the pamphlet¹ to which your leading article (12 November, p 1244) refers may I be allowed to correct some misinterpretations and extend the discussion a little?

You question the validity of our logic on the ground that our premises were not correct. Quite apart from a certain confusion about the difference between a premise and a conclusion, I think your readers would doubt that anyone could adopt as a starting point the existence of "an exact relationship between quantity of surgery and the size of non-medical or economic reasons for operation" (my italics). We certainly did no such thing—we simply pointed to the empirical evidence indicating a positive association, which is quite different. That does not prove causation, nor does it