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

necessarily imply that "where intervention is frequent clinical standards are necessarily low." All this was discussed in our pamphlet with much supporting evidence, amply quoted.

It is not difficult to deny our conclusions in a leading article claiming highly dubious premises to be the basis for our argument. What we argued was quite simply that where large variations in surgery rates exist it is important to know whether or not any of the variation is caused by essentially inappropriate (that is, non-medical) considerations. If it is, then it is important to know whether the higher rates usually associated with fee-for-service medicine are more appropriate than the lower rates of the NHS or prepaid practice. That is why we devoted some space to evaluation of these issues by clinical trials and quoted some examples where high rates may not be appropriate. We also discussed some work attempting an evaluation of the costs, risks, and benefits of surgery² to throw some further light on this difficult problem. Unfortunately there is no space here to go through the arguments, which anyway suffer too much from simplistic polarisations.

We also stressed that the process of evaluation was rarely easy for a whole series of reasons to do with the organisation of medicine and for legitimate scientific or ethical considerations. An example of one of the difficulties is provided by your quotation of one recent study³ of the relationship between rates and "clinical standards." It is, however, one among many studies looking at the variations in rates of surgery and one among a few studies of the relationships between rates and standards. To suggest that this study is puzzling implicitly recognises the validity of our argument, for it finds no negative association between rates of tonsillectomy (TA) in Manitoba and clinical standards. The proportion of these operations which had a particular set of clinical indications was no lower in areas with a higher rate. However, it is the core of your evidence suggesting our inference to be weak. We actually cited much more evidence pointing in the opposite direction, particularly for dentistry as well as diagnostic tests and surgery. We could not then discuss this paper because it was not published.

However, it ought to be noted that since interest in surgical rates has received more publicity several things have happened to TA rates in North America. In Canada these rates have dropped by over 30% since 1968⁴ and Manitoba, during the period of the above study, had the second lowest rates of all Canadian provinces (these are using total population as a denominator but are age-standardised). The lowest province, Newfoundland, happened to have the lowest rates for all the other seven common procedures which were reported. Most important, however, there has been a more dramatic reduction in the variation of these rates over the same time. A study in Vermont, USA,⁵ shows that since information on rates has been reliably collected and fed back to clinicians not only has the TA rate declined by 46% over the state but the variation between hospital service region of residence has decreased by a factor of nearly four between 1969 and 1973 measured by the standard deviation of the rates. Obviously many factors may contribute to this reduction, not least of which is the estimate that the highest rate in 1969 left only 37% of children⁶ with any tonsils. The fact remains that for whatever reason the variation in rate has reduced in Canada too and in Manitoba it was less than the variation in Vermont even in 1973.

It is a basic principle of good experimental design that to test an aetiological hypothesis of a given factor on another one is ill advised to take as one's sample a set of observations known to vary less than does the "population" for which one would want to make an inference. For example, if one wants to investigate the possible role of dietary fibre

intake on the prevalence of diseases of the colon one would try not to rely too heavily on information based on a group of people known to have, relative to the entire population, similar dietary habits. What we were discussing were those otherwise comparable areas for which the variations in levels of practice were higher than any variation in legitimate index of medical need could explain, of which there are many. TA rates in Manitoba in 1973 did not happen to be among them and the results of that study are not, in the end, all that puzzling.

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¹ Radical Statistics Health Group, In *Defence of the NHS*. London, RSHG, 1977.

² *Costs, Risks, and Benefits of Surgery*, ed J Bunker, B Barnes, and F Mosteller. London, Oxford University Press, 1977.

³ Roos, N P, Roos, L L, and Hanteleff, P D, *New England Journal of Medicine*, 1977, **297**, 360.

⁴ Vayda, E, Morison, M, and Anderson, G, *Canadian Journal of Surgery*, 1976, **19**, 235.

⁵ Wennberg, J, et al, *Pediatrics*, 1977, **59**, 821.

⁶ Wennberg, J, and Gittelsohn, A, *Science*, 1973, **182**, 1102.

Dietary cholesterol and atherosclerosis

SIR,—In their survey of diet in relation to coronary heart disease (19 November, p 1307) Professor J N Morris and his colleagues found that "analysis of dietary cholesterol against coronary events showed no association at all." In this connection I wonder how many of your readers could give the author and date of the following quotation.

"Among other factors that may play an important part in the pathogenesis of atherosclerosis attention has recently often been drawn to the importance of an increased amount of cholesterol in the organism in general and in the blood in particular. As is well known, an attempt has even been made to set up a theory of the origin of atherosclerosis that rests solely on hypercholesterolaemia.

"The most important facts that form the basis of this and similar theories are the following. Firstly, one often finds a more or less raised blood cholesterol content in cases of human atherosclerosis. Secondly, the wall of the atherosclerotic aorta always contains an increased amount of cholesterol or of its compounds, which apparently play a large part in the origin and development of the atherosclerotic changes. Thirdly and last, it is possible to produce typical atherosclerosis in rabbits by prolonged feeding of cholesterol-rich foods or of pure cholesterol.

"The two first of these arguments do not have the force of direct and incontrovertible proof since hypercholesterolaemia, although often accompanying the obvious cases of atherosclerosis, does not appear to be an absolutely constant finding in atherosclerosis. Cholesterol deposits in the aortic wall as well as hypercholesterolaemia may also be looked upon simply as a concomitant phenomenon in atherosclerosis. Moreover, the occurrence of cholesterol in the aortic wall may be considered, as has already been done by several writers, simply as being derived from breakdown products of the already pathologically altered components of the aortic wall.

"In contrast, the third of the above-mentioned arguments can to some extent be accepted as a direct proof for the 'cholesterol aetiology' of atherosclerosis. If it is in fact possible to produce typical atherosclerotic changes in the aorta of rabbits by the administration of pure cholesterol without any other harmful factor, then it seems that this is proof that the development of atherosclerosis depends entirely on the content of cholesterol or of its compounds.

"It is, however, possible to find important objections to a direct transfer of these experimental results to man. Firstly, in order to produce experimental atherosclerosis by feeding rabbits with

cholesterol colossal doses are needed. In association with this the cholesterol content of the blood in these rabbits reaches enormous values. On the other hand human beings never consume these quantities of cholesterol and never does the amount of cholesterol in the blood of human beings, even in the severest degree of hypercholesterolaemia, reach such enormous values as in animals that have been fed with cholesterol for a long time. . . ."

This was written by Anitschkow in a paper published in 1914¹ which I have translated from the German. It appeared one year after his classic paper² describing the first experimental production of atheroma, by feeding rabbits with cholesterol.

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¹ Anitschkow, N, *Deutsche medizinische Wochenschrift*, 1914, **24**, 1215.

² Anitschkow, N, and Chalotow, S S, *Zentralblatt für allgemeine Pathologie und pathologische Anatomie*, 1913, **24**, 1.

Treating dissenters

SIR,—Dr Edward Hare in his article on dissenters (29 October, p 1136) refers to the historical background of psychiatric abuse in Russia and accepts that it has become more common in that country in the past 25 years. This psychiatric abuse as practised both in the past and at the present time consists essentially in diagnosing an individual held to be politically undesirable as mentally ill when this is not the case and then proceeding to deprive him of his liberty by incarcerating him for an indefinite period in a special or prison mental hospital. There can be surely no greater abuse of medicine than this and it can be perpetrated only with the active co-operation of the psychiatrist. It must be seen to be what it is—namely, an act of political repression masquerading as medical treatment.

This is tacitly admitted when Dr Hare states that Soviet politicians might argue that they are acting with as much humanity as possible in a collectivist society against persons whose behaviour constitutes a serious threat to the stability of government. To suggest that this action of quite unwarranted commitment to a mental hospital is a humane alternative to a defined term in prison merely adds insult to injury. And the further comment of Dr Hare that although treatment is in some cases against the will of the individual, yet it is no different from that given to a patient with the same diagnosis ignores the fact that he should not have been forced there in the first place and is no great source of consolation to the victim convinced of his own sanity.

Such dissidents, Dr Hare feels, behave as they do either because of a fearless and noble love of truth or from an obstinate determination to speak one's mind. Is it possible that it could be for both reasons? This obsessive persistence, as he terms it, in the face of warnings and threats could well be applied to the men of destiny and the martyrs of history down the ages and his apologia for the Soviet psychiatrists acting under pressure from the State could equally well apply to the infamous Nazi doctors of the concentration camps.

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SIR,—Dr Edward Hare's summary under the heading "Evidence of guilt" (29 October, p 1136) is clear and helpful. However, under