four to five hours before the blood sample is taken. Failure to take this precaution may result in fluctuating results.—We are, etc.,

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Fractures and Fluoride

SIR,—Opponents of water fluoridation are already quoting the results reported by Dr. J. Inkovaara and others (12 July, p. 73) as proof that fluoride causes fractures in old people. Before this assertion passes into the popular mythology of the antifluoridation movement there are a number of pertinent points to be made.

The fluoride intake of patients in the group given prophylactic treatment by the Finnish workers was the equivalent of drinking 25 litres (44 pints) of water at 1 p.p.m. F each day for five months and 25 litres each day on two days every week for a further three months. The reader can judge how relevant this regimen could possibly be to water fluoridation.

Patients with known osteoporosis were included in the trial but the report does not say how many were in the group given prophylactic fluoride treatment and how many were in the control group, nor how many of the fractures were sustained by these osteoporotic patients. Nevertheless, the authors believe that fluoride was "probably partly responsible" for the fractures in the treatment group but it is doubtful whether this view, cautious though it be, is upheld by the evidence. The incidence of fractures in the elderly increases exponentially with age. The mean age may not therefore be the appropriate statistic to use in order to demonstrate that the treatment and control groups were comparable with respect to this important variable. In one respect the groups were certainly not comparable: 83% of the treated patients were women compared with 74% of the controls. Since the incidence of fractures among elderly women is two to three times that of elderly men of the same age one would expect, on this basis alone, more fractures in the treatment group than among the controls.

It is difficult from the information in the paper to determine which denominators should be used in seeking to assess how significant is the excess of five fractures in the treatment group over the course of the trial. Assuming that all patients with fractures were hospitalized there were 42 patients in the treatment group and 35 controls hospitalized for other reasons. Subtracting these numbers and the numbers "discontinued" from the numbers at onset would leave 157 in the treatment group and 175 controls. The distribution between the two groups of the 17 fractures that occurred during the trial could easily have arisen as random variation (χ^2 with Yates's correction = 1.51; $0.2 < P < 0.3$).

It is not clear how much account should be taken of the three fractures that occurred in the treatment group in the month after the trial was ended. How many fractures occurred in each group the following month and the month after that? The trial ended in January 1972, and one would wish to have rather more information about the subsequent experience of the two groups in a report than appears in print three and a half years later. But even if these late fractures are added to the number of earlier ones, using the same denominators as before, the difference between the groups in the frequency of

fractures is still not significant at the conventional 5% level (χ^2 with Yates's correction = 3.49).

In one respect the results reported were reassuring. They indicate how rapidly the free ionized fluoride levels in plasma came to approximate the control level in elderly persons receiving 50 mg fluoride a week additional to their diet, having previously been given relatively massive doses (25 mg a day) for five months.—I am, etc.,

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Prolactin, Bromocriptine, and Haemostasis

SIR,—In the past two years we have treated large numbers of rats, guinea pigs, and mice with prolactin and the prolactin-suppressing drug bromocriptine. We have repeatedly noticed that blood from prolactin-treated animals clots very rapidly, and this has caused problems in the conduct of experiments. We have just attempted to quantify this effect by making observations on 40 Balb/c mice.

Ten mice were treated for 14 days with control saline injections, 10 with 500 μ g/day ovine prolactin, 10 with 500 μ g/day bromocriptine, and 10 with both prolactin and bromocriptine. Under ether anaesthesia the terminal 1 cm of tail was cut off. With the tail hanging down the blood was allowed to drip. The drops were removed by filter paper without touching the tail itself until the bleeding stopped. After one minute of bleeding three drops were collected on a clean microscope slide, which was then rocked backwards and forwards at room temperature until coagulation occurred. The results are shown in the table.

Effects of various treatments on bleeding time and whole blood coagulation time in Balb/c mice. Bleeding time was taken as the time from collecting first drop of blood to coagulation. Results expressed in seconds $\pm$ S.E.M.

Treatment	Bleeding Time	Coagulation Time
Control saline	353 $\pm$ 42	371 $\pm$ 22
Prolactin 500 μ g/day	305 $\pm$ 55	211 $\pm$ 21
Bromocriptine 500 μ g/day	192 $\pm$ 30	359 $\pm$ 36
Prolactin + bromocriptine	236 $\pm$ 26	373 $\pm$ 21

Prolactin shortened the bleeding time by a non-significant amount whereas both bromocriptine ($P < 0.025$) and prolactin + bromocriptine ($P < 0.05$) shortened it significantly. Only prolactin given alone had any effect on the coagulation time, which was highly significantly reduced ($P < 0.001$).

We recognize that sophisticated techniques are required for the full investigation of changes in haemostasis and coagulation. We are not in a position to follow up this work but we hope someone else may do so. Prolactin levels are raised during surgery,¹ admission to a coronary care unit,² and oral contraceptive therapy,³ so the effects could have clinical significance. We wish to point out that bromocriptine opposed the action of injected prolactin on coagulation and so could not have been working by suppressing prolactin secretion. We have argued elsewhere that bromocriptine may block prolactin actions peripherally as well as suppressing its secretion centrally,⁴ and these results support that view.

We thank Professor E. Flückiger of Sandoz, Basel, for the bromocriptine and the North of England Cancer Campaign and the Ernest Hart

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—We are, etc.,

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Hormones, Elderly Testes, and Carcinoma of the Prostate

SIR,—Your leading article (5 July, p. 2) rightly draws attention to the wide variation in Leydig cell function found in men of advanced years but does not indicate the possible significance of these findings in the management of carcinoma of the prostate. Hormonal manipulation with oestrogen therapy or bilateral orchidectomy is widely used in the treatment of advanced prostatic cancer, but as yet no attempt is made to assess the testicular function of the patient before therapy is commenced. Though there are individual patients whose symptoms and signs respond dramatically either to bilateral orchidectomy or to oestrogen administration, there are also patients whose tumour does not respond to hormonal therapy.

We have found a wide variation in the Leydig cell function (as measured by serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) concentrations) of elderly men presenting with untreated carcinoma of the prostate. Our preliminary unpublished results show that some patients have good Leydig cell function comparable to that observed in young men. Others, however, have a hormone profile similar to that observed after castration. During the week after bilateral orchidectomy there is a dramatic fall in the concentration of testosterone and the concentration of LH and FSH is increased in the patients with normal Leydig cell function, but, as might have been expected, there is little or no change in the already abnormal concentrations of testosterone, LH, and FSH in men with pre-existing Leydig cell failure.

Provided that the tumour is intrinsically hormone dependent it seems reasonable to suggest that the response of carcinoma of the prostate to orchidectomy, and possibly administration of oestrogens, should correlate with the degree of hormonal deficit created by therapy. We are currently testing this hypothesis in a study designed to determine whether the response of carcinoma of the prostate to orchidectomy or oestrogen administration is dependent on the initial Leydig cell function of the patient and whether routine measurement of the concentrations of testosterone, LH, and FSH in serum might provide a basis for identification of those patients whose tumour will respond to hormone manipulation.—We are, etc.,

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