

was normal. On admission to our unit the white cell count was  $0.4 \times 10^9/l$  with no neutrophils. She remained agranulocytic for six days after the aminoglutethimide was stopped. Six days after admission the platelet count fell from  $230 \times 10^9/l$  to  $30 \times 10^9/l$  and remained below  $100 \times 10^9/l$  for a further 11 days. The haemoglobin fell to 79 g/l from 120 g/l without evidence of haemolysis or haemorrhage. She was treated with broad spectrum antibiotics and steroids and was discharged after 35 days with haemoglobin 89 g/l (8% reticulocytes), white cells  $12 \times 10^9/l$  (50% neutrophils), and platelets  $180 \times 10^9/l$ . For seven years she had been treated without complication with betanidine, metoprolol, and a thiazide diuretic for hypertension. Her case has been reported to the Committee on Safety of Medicines.

The rationale for the use of aminoglutethimide in postmenopausal breast cancer is that it reduces adrenal sex hormone production by inhibiting conversion of cholesterol to pregnenolone. Hydrocortisone is given to prevent an Addisonian crisis and also a compensatory rise in adrenocorticotrophic hormone, which would overcome the enzyme inhibition.<sup>1</sup> However, at a dose of 40 mg/day hydrocortisone would be expected to inhibit adrenocorticotrophic hormone secretion and reduce adrenal steroid secretion without the need for aminoglutethimide, and indeed similar changes in hormone secretion have been reported with hydrocortisone alone.<sup>2</sup> It would appear to be mandatory that in future trials aminoglutethimide with hydrocortisone is compared not only with placebo but also with hydrocortisone alone particularly as the incidence of side effects with aminoglutethimide is high.<sup>1</sup>

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- 1 Santen RJ, Lipton A, Harvey H, Wells SA. Use of aminoglutethimide and hydrocortisone as a "Medical Adrenalectomy" for treatment of breast carcinoma. *Prog Clin Cancer* 1982;8:245-65.
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### Relation between recurrence of cancer and blood transfusion

SIR,—We read with interest the letter of Mr David Francis and Mr Rodney Judson (24 August, p 544) commenting on the paper of Professor Neil Blumberg and others.<sup>1</sup> We have examined the survival of 67 patients undergoing nephrectomy for adenocarcinoma of kidney. The patients were treated from 1976 to 1984 in the Western Infirmary, Glasgow. Thirty nine patients received blood or packed red cells (mean 3 units) during their hospital stay at the time of surgery. We could detect no statistical difference in the age or sex composition of the two groups. Similarly, the proportions presenting with haematuria did not differ between the groups. A haemoglobin level of less than 100 g/l did appear to predispose to transfusion but values greater than 100 g/l did not influence transfusion practice.

Retrospective staging was assessed using both the Robson<sup>2</sup> and the Union Internationale Contre le Cancer<sup>3</sup> classifications. There was no statistically significant difference in terms of either classification. There was a survival advantage in the non-transfused group, of whom 58% were alive at the end of the study compared with 48% of those transfused ( $\chi^2 = 3.06$ , 1 df;  $p = 0.08$ ). We are aware that analysis of a small number of patients may obscure some real difference between our transfused and not transfused groups. Despite apparent comparability of stage and other variables, our findings might reflect, for example, the degree of

operative difficulty. The survival difference may, however, have an immunological basis and we believe this to be the first report of this effect in patients with renal carcinoma. The observation requires further elaboration and we support the suggestion by Messrs Francis and Judson that prospective studies should be established.

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- 1 Blumberg N, Agarwal MM, Chuang C. Relation between recurrence of cancer of the colon and blood transfusion. *Br Med J* 1985;290:1037-9.
- 2 Robson CJ, Churchill BM, Anderson W. The results of radical nephrectomy for renal cell carcinoma. *J Urol* 1968;101:297-301.
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### Do locum duties help or hinder acquisition of clinical knowledge by final year medical students?

SIR,—Mr Nicholas Banatvala's letter (14 September, p 740) highlights an important deficiency in the present clinical teaching programme. I undertook an overseas student elective in San Francisco at the University of California some years ago. Together with their own senior medical students, I was allotted a small number of patients to care for and acted as junior intern under the supervision of the resident medical team. Those three months were probably the most useful in the whole of the clinical curriculum, providing exposure to those situations that the newly qualified houseman faces the day he qualifies. With supervision, this is the best form of practical training that could be given to the final year student. Coming back to London, I found the standard studentship dull and very theoretical.

Teaching clinical students has been my regular duty over the years. Even today I find most students competent in theoretical knowledge but still badly lacking practical experience. What we should be planning is a regular period of "junior housemanship" for final year students. Student locums are not only spasmodic but also enjoyed only by a fortunate few. Without doubt the neomedic would be a better doctor having been given the practical exposure he so sorely needs today.

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### Do sex hormones affect colorectal cancer?

SIR,—Dr Michael Davidson and colleagues (22 June, p 1868) point out several reasons for believing that right sided cancer of the colon may be associated with sex hormones and report a strong association between subsite and stilboesterol treatment in 26 men with prostatic cancer who subsequently developed cancer of the colon. In a

further effort to examine the relation we have tabulated the site distribution of 162 cases of colon cancer occurring in 1978-83 among men and women aged 45 to 64 at the Group Health Cooperative of Puget Sound, located in Seattle, Washington, and collated this information with computerised data on drug purchases by Cooperative members. Use of conjugated oestrogen, lethinylestradiol, and diethylstilboesterol within five years of diagnosis was examined, including only those prescriptions which were refilled at least once. No man who subsequently developed cancer of the colon received any oestrogens. The site distribution determined from ICD discharge codes of 81 women who either had never used conjugated oestrogens or were repeated users of them and who had a determinable subsite is shown in the table.

Patients with cancers of the right side of the colon formed very similar percentages of the user and non-user populations. There were no repeat users of either ethinylestradiol or diethylstilboesterol among the patients with cancer of the colon. The odds ratio comparing right sided (ICD 153.0 + 153.1) with left sided (ICD 153.3 + 153.4) colon cancers in repeat users versus never users of conjugated oestrogens was 0.7 with a 90% exact confidence interval of 0.3 to 2.8.

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### Smoking, sugar, and inflammatory bowel disease

SIR,—Following the letter by Dr E Stermer and others (17 August, p 487) on the negative correlation between smoking and ulcerative colitis, we would like to report the results of a study we have carried out on outpatients.

We evaluated not only smoking habits but also the intake of refined carbohydrates and vegetable fibre in 124 patients suffering from ulcerative colitis, 109 patients with Crohn's disease, and 250 controls matched by sex and age (within the same five year span) devoid of gastrointestinal and neoplastic disease.<sup>1,2</sup>

Ulcerative colitis was more common among ex-smokers (patients who had stopped smoking at least one year before the onset of the disease), relative risk (RR = 2.6;  $p < 0.05$ ). A seemingly protective effect of smoking in this disease was brought to light also by analysing the incidence of ulcerative colitis among people who smoked more than 15 cigarettes/day (RR = 0.3;  $p < 0.003$ ).

Conversely, a positive correlation was found between smoking and Crohn's disease: the risk was 3.7 times greater among smokers than among non-smokers ( $p < 0.05$ ). Both these diseases were positively correlated with refined carbohydrate intake: a high intake of sugar increased the risk of contracting ulcerative colitis or Crohn's disease by a factor of 2.37 and 2.38 as compared with normal consump-

### Subsite distribution of cancer of colon in women at Group Health Cooperative of Puget Sound 1978-83

	Site (ICD, 8th revision)				
	Cecum (153.0)	Ascending (153.1)	Transverse (153.2)	Descending (153.3)	Sigmoid (153.4)
Conjugated oestrogens					
Never users	13	4	6	8	29
	28.3%				
Repeat users	5	0	4	0	12
	23.8%				

tion; a notable intake of bread increased the risk further, up to 6.38 and 3.76 times respectively. In contrast, a considerable intake of vegetables and fruit seemed to reduce the risk (RR for Crohn's disease = 0.36 and 0.66; RR for ulcerative colitis = 0.30 and 0.38).

Our data confirm not only the negative correlation between smoking and ulcerative colitis<sup>1</sup> but also the positive correlation between refined carbohydrate consumption and inflammatory bowel disease and the seemingly protective effect of vegetable residue on these diseases.<sup>4</sup>

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- 4 Thornton JR, Emmett PM, Heaton KW. Smoking, sugar, and inflammatory bowel disease. *Br Med J* 1985;290:1786.

### MRC trial of treatment of mild hypertension

SIR,—We would like to question the adequacy of the characterisation of blood pressure at entry into the recently published MRC trial<sup>1</sup> (13 July, p 97). This may have bearing on the low benefit found in that trial from treating mild hypertension.

In the trial 43% of the male and 50% of the female placebo takers at the end of five years had diastolic pressures below 90 mm Hg. This was not due to a placebo response to the inert tablets because it was also seen in 288 patients randomly assigned at entry to a regimen of observation only, taking no tablets but otherwise adhering to the trial protocol. Only 32% of placebo takers had no measurement of diastolic pressure below 90 mm Hg at any of the annual visits. This percentage would apply also to those who entered the treated group. Hence only about 4600 of the 18 000 patients studied were consistently in the intended blood pressure range.

Characterisation of blood pressure in the trial was by six blood pressure readings, two readings on each of three different occasions. The first four readings were taken by specially trained nurses and the last two by a medical practitioner. The fact that a doctor took the last two readings may have acted as a stress stimulus, provoking spuriously high readings. There is some evidence of this in an earlier paper,<sup>1</sup> where fig 5 shows a slight rise in systolic pressure between "screening" and "entry" and then a precipitous fall in blood pressure in the control group between "entry" and the next follow up examination.

At the Dunedin Hypertension Clinic the single lying and standing blood pressure readings by the examining doctor at initial assessment are invariably higher than the average of readings taken

over a morning (four readings over two hours) or a full day (seven to eight readings over five to six hours) by trained technicians (see table). The mean of four blood pressure readings taken over time (two hours at least) is also a much better predictor than a casual reading of the 24 hour blood pressure average.<sup>2</sup>

Thus in the MRC trial better characterisation of blood pressure might have been achieved if after the two pairs of screening casual blood pressure readings "entry blood pressure" had been the mean of four readings over two hours rather than the mean of two consecutive casual readings. The selection method used resulted in the study of milder hypertension than the intended one of 90-109 mm Hg diastolic. In fact the mean blood pressure, as judged from the values for the control group, seems to have been about 150/92 mm Hg. This needs to be taken into account when the results are applied to everyday practice.

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- 1 MRC Working Party on Mild to Moderate Hypertension. Randomised controlled trial of treatment for mild hypertension: design and pilot trial. *Br Med J* 1977;iii:1437-40.
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### Increase of oleic acid in erythrocytes associated with malignancies

SIR,—In reply to the question raised by Dr Su Metcalfe and others (14 September, p 740), all patients with cancer included in our study had their blood samples taken before blood transfusion, chemotherapy, or radiotherapy. We evaluated 30 samples from the blood bank and there was no difference between the stearic:oleic ratio of the erythrocyte membrane between this group and the normal control group included in the study. We have not investigated, yet, the effect of blood transfusion, chemotherapy, and radiotherapy on the erythrocyte membrane. However, our preliminary data show that interferon reverses the desaturation process in patients with hairy cell leukaemia.

The proposed hypothesis that the tumour releases a desaturation producing factor into the systemic circulation and subsequently in the urine has support from another two facts: firstly, the desaturation observed in malignant cell membranes in human liver neoplasms compared with non-tumour cells<sup>1</sup> and, secondly, the fact that the urine protein concentrate of patients with cancer induced the desaturation of baby hamster kidney cultured cells in vitro. This phenomenon was not observed when the cells were treated with urine protein concentrate from normal subjects or patients without cancer (unpublished data).

Therefore, we speculate that desaturation

producing factor is secreted by the tumour cells and causes desaturation of their own cell membranes. In addition it is released into the systemic circulation and causes enhancement of the stearic acid desaturation of the red blood cell precursors in the bone marrow. Its subsequent appearance in the urine is responsible for the desaturation effect observed in cultured cells treated with urine protein concentrate.

Since the submission of our manuscript (20 July, p 163) our group have found a similar enhancement of stearic acid desaturation of the erythrocyte membrane during the induction of colorectal tumours in rats.

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- 1 Wood CB, Habib NA, Apostolov K, et al. Reduction in the stearic to oleic acid ratio in the human malignant liver neoplasms. *Europ J Surg Oncol* (in press).

### Economics of coronary artery bypass grafting

SIR,—In response to my letter Professor Alan Williams (14 September, p 736) manages to avoid all mention of my principal critique of his article—viz, the lack of any justification of his claimed "powerful methodology." Indeed, it would seem from his concluding parable that he is still searching in the dark for the key.

Incidentally I do not (did not) deny that economic choices are inescapable in health care planning. I am also aware that Sweden faces economic constraints. However, I am sure that my NHS colleagues, cash limited and RAWPed as they are, would be much happier making choices at the level of health care expenditure customary in Sweden. The guns and butter remark arose from the International Institute of Strategic Studies 1983-4 estimates of defence expenditure, which were \$18.9 billion in West Germany and \$17.9 billion in the UK. If we spent the same as West Germany and devoted even part of the difference to health care then some painful choices would become redundant. And we might be able to restore some of the capital sums which successive governments have denied the NHS.

To return to Professor Williams' parable, I think the real difference between us is that I am very doubtful that he will find a master key, wherever he looks. Decisions on health care expenditure, whether at macroeconomics or microeconomic level, are based on a mix of inadequate, often questionable data, ideology, fashion, and value judgment, influenced by previous decisions and haste. If that is "romantic escapism" then I plead guilty.

"Measures of outcome," a generic term that subsumes Professor Williams' suggested techniques, are currently preoccupying people from various disciplines, not only for resource allocation but also for quality control purposes. Such measures are clearly needed in the NHS, and no doubt the new breed of managers will stimulate their development. However, given the long and still evolving history of the most potent measure of outcome so far devised—the randomised trial—which often proves unsatisfactory for decision making, I foresee a long period of development and validation before any of these new methodologies will deserve the adjective "powerful."

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Comparison of mean values (SD) for presenting blood pressures (mm Hg) in 674 untreated hypertensive outpatients referred to the Dunedin Hypertension Clinic during 1964-83 taken as casual single reading (1st casual) and as series of 4-8 readings over 2-6 hours (1st daytest mean).

	No	Variable	Lying		Standing	
			1st Casual	1st Daytest mean	1st Casual	1st Daytest mean
Men	325	Systolic	177 (30)	164 (26)*	169 (28)	155 (24)*
	325	Diastolic	105 (21)	96 (18)*	109 (18)	102 (16)*
Women	349	Systolic	183 (34)	170 (26)*	173 (32)	157 (28)*
	349	Diastolic	107 (19)	98 (17)*	109 (18)	101 (16)*

\* paired t test, p < 0.001.