(Juel-Jensen's syndrome?)? Perhaps this explains the lack of concern about the unpalatability of heavily chlorinated water. I still maintain that flavouring is "very well worth while" when trying to force fluids into an anorexic, nauseated, uncooperative, delirious, and dehydrated patient.

May I also thank Dr D L Child and his colleagues (14 October, p 1086) for their suggestions, which I accept? A parenteral form of chloroquine should have been included and its omission was a transcription error on my part. Chloramphenicol is undoubtedly useful, though I am less sure of co-trimoxazole in patients who have taken Streptotriad prophylactically.

Finally, I would prefer to prescribe Nystaform-HC (nystatin, iodochlorhydroxyquin, and hydrocortisone) to clotrimazole, since the former rapidly alleviates the common allergic component of candidiasis, but this is a quibble.

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¹ Edsall, G, in *Clinical Aspects of Immunology*, ed P G Gell, R R Coombs, and P J Lachmann, 3rd edn. Oxford, Blackwell Scientific, 1975.

² Carpenter, C C J, in *Harrison's Principles of Internal Medicine*, ed G W Thorn et al, 8th edn. New York, McGraw Hill, 1977.

³ Davidson, S, et al, *Human Nutrition and Dietetics*, 6th edn. London and Edinburgh, Churchill Livingstone, 1975.

Razoxane in treatment of acute myeloid leukaemia

SIR,—Drs M Bhavnani, K Dhir, and I W Delamore (16 September, p 801) found the combination of razoxane and cytosine arabinoside (raz/ara-C)¹ ineffective in acute myeloblastic leukaemia (AML). They also found that the combination produced nausea and vomiting in all of their 17 patients. At a meeting at the Westminster Hospital on 9 March 1978 at which Dr Delamore first gave these results five other groups presented their experience with raz/ara-C in 27 patients with AML. Seven of these patients had a complete remission and a further 10 had partial remissions (reduction in bone marrow blasts (but still above 5%), decrease in organomegaly, normal blood counts, and an increase in patient wellbeing). A total of 64% of these 27 patients therefore benefited from the combination of raz/ara-C. In further contrast to Dr Delamore's findings marked nausea, but without vomiting, was seen in only three of the 27 patients.

It is difficult to know why patients at one centre seem not to tolerate treatment which in other centres presents no problems. Since razoxane is given by mouth, however, gastrointestinal intolerance could well influence the effectiveness of the drug. The drop in leucocyte count following administration of raz/ara-C is no guide as to whether razoxane was well absorbed or not, since the blood level of this drug required for depression of the leucocyte count may be less than that required to eliminate blast cells.

On the basis of the results of the five centres referred to (to be published elsewhere), as well as other results, it would seem that raz/ara-C may be indicated as first-line treatment for AML when the supportive care required for the anthracycline induction regimens is not easily available, when patients are at risk through age or infirmity by being exposed to the anthracyclines, or when it may be necessary to attempt to get patients into remission as outpatients. Raz/ara-C could be considered as second-line treatment when other more aggressive regimens have failed. In this

connection it is worth noting that at a paediatric centre (not included in the five centres already mentioned), of four children with acute lymphoblastic leukaemia who had exhausted all the UKALL treatments, two nevertheless went into complete remission on raz/ara-C.

The combination of raz/ara-C can bring down the number of peripheral blood blast cells very quickly without necessarily affecting bone marrow blasts and it may be that such treatment, which must at the very least reduce the leukaemic cell body burden, would make the task of subsequent treatment with any of the more usual AML regimens that much easier. The result might not necessarily be seen in higher remission induction rates or even smoother and quicker inductions but in the duration that such remissions last.

Raz/ara-C may also be a useful alternative to consider for the maintenance of AML remissions, which are often disappointingly short. There is the further possibility that if an all-oral maintenance regimen is essential razoxane and 6-thioguanine might well be a useful combination.

May I lastly clear up some confusion about the mechanism of inhibition of cell division by razoxane. The drug blocks cell cycle progression in late G₂M³—that is, after DNA synthesis is completed. From this and other evidence it is clear that the unsupported statements by Dr Bhavnani and his colleagues that razoxane inhibits cell division by interference with RNA or DNA synthesis or action are at best improbable and almost certainly incorrect. If anything, razoxane stimulates DNA synthesis² in contrast to almost all other anticancer drugs, some of which, like ara-C, very efficiently block DNA synthesis. Raz/ara-C might therefore be particularly appropriate if given together in rapidly proliferating malignancies such as the acute leukaemias, though the timing of administration of the two drugs relative to each other as well as the sequence and dosage could be as important here as they have been under experimental conditions (unpublished observations).

In view of its lack of toxicity on cells it is not surprising that razoxane is the least toxic of all anticancer agents available at present. I hope you will therefore allow me to correct the impression given by the paper of Dr Bhavnani and his colleagues.

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¹ Hellmann, K, et al, *Current Chemotherapy*, p 1178. Washington, DC, American Society for Microbiology, 1978.

² Hellmann, K, et al, *British Journal of Cancer*, 1978, 37, 479.

³ Sharpe, H B A, Field, E D, and Hellmann, K, *Nature*, 1970, 226, 524.

⁴ Hallows, R C, West, D G, and Hellmann, K, *Nature*, 1974, 247, 487.

⁵ Grieder, A, Maurer, R, and Stähelin, H, *Cancer Research*, 1977, 37, 2998.

SIR,—We read with great interest the paper by Dr M Bhavnani and others (16 September, p 801), and would like to report our experience with the use of razoxane in three previously treated patients.

Case 1. A 53-year-old man with acute myelomonocytic leukaemia was treated with eight courses of Barts III followed by four courses of TRAP, five courses of COAP, then fortnightly courses of cyclophosphamide 150 mg and thioguanine 160 mg by mouth for five days. When remission was not achieved it was decided to change to three-day courses of razoxane 125 mg thrice daily at two-weekly intervals. The leucocyte count was $15.8 \times 10^9/l$ ($15\,800/mm^3$) with 80% blasts. After five courses of such treatment the count had risen to $133 \times 10^9/l$ ($133\,000/mm^3$) with 93% blasts and the patient died 26 months after diagnosis.

Case 2. A 36-year-old man with acute myeloblastic leukaemia was in complete remission after six courses of Barts III regimen. He was started on immunotherapy and monthly courses of cytosine arabinoside and thioguanine. He relapsed while on treatment 20 months after diagnosis. It was decided to treat him with razoxane 125 mg thrice daily and cytosine arabinoside 90 mg intravenously, both for three days, with nine-day treatment-free intervals between courses. His leucocyte count at the beginning of this treatment was $2.5 \times 10^9/l$ ($2500/mm^3$) with 1% blasts and the bone marrow was hypercellular with 56% blasts. After four courses of cytosine and razoxane the count was $3.3 \times 10^9/l$ ($3300/mm^3$) with 16% blasts and his marrow showed the presence of 90% blast cells.

Case 3. A 61-year-old woman with Ph¹-negative chronic granulocytic leukaemia was treated with busulphan. Six months later she developed a blast cell crisis. She was treated with 6-mercaptopurine 50 mg daily and prednisolone 30 mg daily for four months. As this therapy was not successful she was started on razoxane as in case 2. At the start of this treatment her leucocyte count was $24.7 \times 10^9/l$ ($24\,700/mm^3$) with 7% blast cells and after two months' treatment with razoxane it was $97.0 \times 10^9/l$ ($97\,000/mm^3$) with 64% blast cells. The patient died 17 months from diagnosis.

In all three patients it was noted that the blast cell count initially dropped at the end of each course of treatment, but by the end of the treatment-free intervals there was a rebound increase in blasts. We conclude from our small series that in the doses described above razoxane is not effective in the treatment of previously treated leukaemic patients. We even go so far as to add that it might be harmful.

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Hormone receptors in breast cancer

SIR,—Your leading article (8 July, p 77) referring to progesterone receptors (PgR) states that "they occur only in patients who are ER-positive." PgR have in fact been reported in patients with breast carcinoma who are oestrogen receptor (ER)-negative.

Raynaud¹ measured ER and PgR in 128 human mammary tumours; he found 16% to be ER-negative, PgR-positive. Pichon² examined 55 human breast carcinomas for ER and PgR and found one of 11 tumours to contain PgR in the absence of ER. Tobin et al³ recently reported that 5 of 80 breast malignancies were found to be ER-negative, PgR-positive. McGuire et al⁴ measured PgR and ER in more than 200 women with breast tumours; they found that PgR was present in 8% of the tumours lacking ER. Degenshein⁵ in a recent paper quotes Wittliff (an oral communication) as identifying ER-negative, PgR-positive cases.

McGuire and his associates have postulated that the presence of PgR in tumour tissue might serve as a more sensitive indicator of endocrine responsiveness since it is known that the synthesis of PgR is controlled by oestrogen in the uterus.^{6,7} Because of the small number of ER-negative, PgR-positive patients who have been reported to date the value of this combination of receptor studies in predicting response to hormonal manipulation has to be determined. However, two investigators have recently reported such preliminary data. King⁸ noted one out of two remissions with hormonal manipulation in patients who were ER-negative, PgR-positive. Bloom⁹ observed

an objective remission in one patient who underwent hormonal ablation and was shown to be ER-negative, PgR-positive.

I hope that the above-cited references will correct the impression that only ER-positive tumours contain PgR. Although the number of cases of PgR-positive, ER-negative tumours is small, they do exist. The importance of recognising this group of mammary carcinomas is that it may provide new insights into the interrelationship that exists between various hormones, their receptors, and tumour regression.

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¹ Raynaud, J P, *Journal of Steroid Biochemistry*, 1975, **14**, 6.

² Pichon, M F, and Milgram, E, *Cancer Research*, 1977, **37**, 464.

³ Tobin, E H, et al, in *Multiple Molecular Forms of Steroid Hormone Receptors*, ed M K Agarwal, p 181. Amsterdam, Elsevier/North-Holland Biomedical Press, 1977.

⁴ McGuire, W L, Horowitz, K B, and DeLaGarza, M, in *Cancer: Trends in Research and Treatment*, ed J C Heuson, W H Mattheim, and M Rozencweig, p 181. New York, Raven Press, 1976.

⁵ Degenshein, G A, et al, *Breast*, 1977, **3**, 29.

⁶ Horowitz, K B, et al, *Science*, 1975, **189**, 726.

⁷ Horowitz, K B, and McGuire, W L, in *Progesterone Receptors in Normal and Neoplastic Tissue*, ed W L McGuire, J P Raynaud, and E E Baulieu, p 102. New York, Raven Press, 1977.

⁸ King, R J B, First Innsbruck Winter Conference on Biochemistry in Clinical Medicine, Innsbruck, Austria, January 1978.

⁹ Bloom, N, Tobin, E H, and Degenshein, G A, in *Progesterone Receptors in Normal and Neoplastic Tissue*, ed W L McGuire, J P Raynaud, and E E Baulieu, p 125. New York, Raven Press, 1977.

* *We would agree that the statement that progesterone receptors occur only in patients who are ER-positive is too absolute. As Dr Appelbaum points out, PgR have been reported in a few ER-negative patients, though it is of interest that there is a clear relationship between the concentrations of oestrogen and progesterone receptors even in those patients who are reported as receptor-positive.¹⁻³ Clinical studies of hormone responsiveness in this small group of patients will be required before the meaning and relevance of such a finding are evident.—ED, BMJ.

¹ Pichon, M F, and Milgram, E, *Cancer Research*, 1977, **37**, 464.

² Horowitz, K B, and McGuire, W L, in *Progesterone Receptors in Normal and Neoplastic Tissue*, ed W L McGuire, J P Raynaud, and E E Baulieu, p 102. New York, Raven Press, 1977.

³ Leclercq, G, et al, in *Progesterone Receptors in Normal and Neoplastic Tissue*, ed W L McGuire, J P Raynaud, and E E Baulieu, p 141. New York, Raven Press, 1977.

Thyroid function tests

SIR,—We read with interest the comments of Mr M G Davies and Dr H Allison and of Dr W A Burr (9 September, p 771) on our paper on thyroid function tests in patients with abnormal concentrations of thyroxine-binding proteins (12 August, p 477).

We agree with Mr Davies and Dr Allison that the free thyroxine index (FTI), whether modified as we suggested or not, may be misleading in patients with very high concentrations of thyroxine-binding globulin (TBG) because of the limitations of the Thyopac-3 technique.¹ To check whether erroneous high values influenced the normal range for our modification of the FTI we recalculated it using data from only those patients with Thyopac-3 values of 120% or less. The 95% limits obtained using the

data did not differ from those for all 200 patients. Thus our reference range remains valid. Their suggestion that a single zero standard will resolve the "zero error" in the conventional FTI is incorrect because of the spread of values at very low thyroxine (T4) and Thyopac-3 values.

We suggested in our paper that further investigation is needed to determine whether the T4:TBG ratio or our modification of the FTI provides the better discriminant for the evaluation of thyroid function in patients with abnormal binding proteins. The original paper by Dr Burr and his colleagues¹ gave data on patients with absent TBG but none on euthyroid patients with such conditions as nephrotic syndrome or chronic liver disease who have measurable TBG values below 5 mg/l. In his letter Dr Burr gives the numbers of false-negative diagnoses for our modification of the FTI, the conventional FTI, and the T4:TBG ratio in 101 patients with thyrotoxicosis and 36 with myxoedema. He concludes that the modified FTI is "almost certainly inferior" to the T4:TBG ratio. However, the diagnostic efficiency of a test depends not only on the false-negative rate but also on the false-positive rate, and both are needed, particularly in patients with abnormal binding proteins, before conclusions can be drawn.

The first-line tests of thyroid function are commonly estimations of either total T4 and thyroid-stimulating hormone or total T4 and triiodothyronine, depending on the clinical situation. It may well be that in those patients in whom measurement of binding proteins is indicated the T4:TBG ratio will provide a better discriminant than our modification of the FTI. However, we believe that this remains to be proved.

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¹ Burr, W A, et al, *British Medical Journal*, 1977, **1**, 485.

Postpartum haemorrhage after induced and spontaneous labour

SIR,—Surgeon Commander P R S Brinsden and Mr A D Clark (23 September, p 855) may be interested in the results of an analysis I made into the relationship between the administration of oxytocics during labour and primary postpartum haemorrhage at this hospital during 1974.

Of the 907 deliveries occurring during that year, 49.2% were induced and 54.1% were preceded by administration of an oxytocic to

induce or accelerate labour. The incidence of primary postpartum haemorrhage, defined as a loss of 500 ml or more within 24 h of delivery, was as shown in the table below.

No relationship was apparent between oxytocin infusion and primary postpartum haemorrhage in primigravidae. In multi-gravidae, however, the relationship may have been clinically significant. The oxytocin regimen used was that described by Normington.¹

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¹ Normington, E A M, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1972, **79**, 1108.

SIR,—I am grateful for the study by Mr P R S Brinsden and Mr A D Clark (23 September, p 855) of the impact of induction of labour on the incidence of postpartum haemorrhage. Indeed, postpartum haemorrhage may be, and too often is, a complication of induced labour. However, one very simple measure—the continuation of the intravenous oxytocic infusion for, say, one hour after the delivery of the placenta (the duration of the "fourth stage" of labour coined by our USA colleagues) is supreme for the prevention of this complication. That hypotonic postpartum haemorrhage is indeed preventable has been clearly shown by our analysis of a consecutive series of about 1700 elective labour inductions by means of low amniotomy and intravenous oxytocin, prostaglandin E₂ or prostaglandin F_{2α}.

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Radiology work load

SIR,—The extraordinary response from Dr M Lea Thomas (2 September, p 706) to my paper on radiology work load (12 August, p 514) has deflected the debate from the central issue.

My objective is a system of radiological practice in which patients derive maximum benefit. My thesis is that each department has a capacity limited by the need to maintain reasonable professional standards. Where demand exceeds this reasonable capacity priorities are determined by consultation with users. Urgent work is done before less urgent, which may have to wait. The length of this wait will diminish if inappropriate requests are not initiated. Although this

Oxytocic administration and postpartum haemorrhage (No of cases)

	Syntocinon infusion		Buccal oxytocin	Dinoprostone oral solution	No oxytocic	
	Primi-gravidae	Multi-gravidae			Primi-gravidae	Multi-gravidae
Total treated	164	143	130	54	144	272
Simple postpartum haemorrhage	4	8	1	1	3	5
Postpartum haemorrhage and forceps delivery	3	—	—	—	4	—
Postpartum haemorrhage and manual removal of placenta	1	1	2	—	—	1
Total postpartum haemorrhage	8	9*	3	1	7	6*

* $\chi^2 = 3.4$; $P < 0.10$.