such monitoring could not be better achieved by direct fetal ECG monitoring after rupture of the membranes. Their suggestion that low-risk cases do not need monitoring under such circumstances must also be questioned.

While prostaglandin given vaginally is undoubtedly effective in achieving cervical softening, be it by the effect of circulating oestradiol or, as we are currently assessing in this unit, by an effect on collagenase activity in the cervix, the response to such treatment is widely regarded as very variable—as noted in this series, where a number of patients laboured after a single administration and some failed to respond to two such administrations of prostaglandin E_2 . Its blanket use in a fixed-dose regimen must be questionable under such circumstances and it must be only a matter of time before the hypertonus already reported recurs with more serious consequences.

The transfer of a patient in labour starting after the administration of prostaglandin E_2 vaginally on the antenatal ward may not be always as rapid and smooth as is necessary if monitoring is to be instituted sufficiently early in labour to avoid occasional fetal asphyxia. A routine induction policy must carry with it some risk and I would be concerned to see it generally applied without the recognition of this problem.

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Thromboembolism in pregnancy

SIR,—In your leading article (23 June, p 1661) the comment is made that "... oral anticoagulants are probably best avoided in the puerperium if the mother is breast-feeding." The most widely used oral anticoagulant in this country is warfarin; we have clearly demonstrated that warfarin is not excreted in human breast milk.¹ Using sensitive and specific analytical techniques, less than 10 ng/ml warfarin was found in breast milk and in the plasma of breast-fed infants. This concentration of warfarin is at least ten times less than that usually required to produce any change in the prothrombin time. Further, no prolongation of prothrombin time was found in those infants breast-fed by mothers taking warfarin. Earlier reports of warfarin being present in breast milk utilised non-specific warfarin assay methods, which monitored inactive warfarin metabolites in breast milk.

Mothers are being encouraged now to breast-feed their infants whenever possible. There is no need to deny this on the basis of outdated and inaccurate information to women taking warfarin.

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¹ Orme, ML'E, et al, *British Medical Journal*, 1979, 1, 1564.

Luteal function in patients seeking AID

SIR,—I can confirm the report of Mr M F Vere and Mr D N Joyce (14 July, p 100) on the effects of stress during artificial insemination by donor (AID) in suppressing ovulation.

I have also noted in the last 30 years that

the wives of sterile men have more problems of irregular menstruation than the wives of fertile men. Nevertheless I have shown^{1,2} that emotional stress can affect some 25% of wives whose husbands are fertile. Where patients have kept preconsultation charts one sometimes sees, in an otherwise normal series, one or two cycles which are poor. Inquiry then elicits the fact that some stress, such as family bereavement or diagnosis of azoospermia, occurred in that cycle. The effects of stress can also be observed in women being treated with bromocriptine, clomiphene, or tamoxifen. For example, a woman ovulates when on holiday, but not when attending for AID or, in another case, when a parent died, and so on.

It would seem therefore that in infertility problems laboratory investigations should not be taken at their face value, but must be studied in relation to the total clinical status of the patient. Hormone assays may well be misleading in these circumstances because of stress, which may not be manifest without close questioning.

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¹ Sandler, B, *Journal of Obstetrics and Gynaecology of the British Commonwealth*, 1961, 68, 809.

² Sandler, B, *Journal of Psychosomatic Research*, 1968, 12, 51.

Drugs for pain

SIR,—The 16 June issue (p 1619) refers to my work in Dr R G Twycross's review of the book by Parkhouse et al entitled *Analgesic Drugs*. Twycross refers to "several debatable American views." I am not sure that I understand why the statement that "morphine is usually given parenterally as its oral activity is low" has "a hollow ring" about it.

I would have thought that in most countries morphine is usually given parenterally. There is certainly no doubt that one has to give seven or eight times the parenteral dose when the oral route is chosen, and even then peak effects are not rapidly achieved or as impressive. Hence in the management of acute pain, which is the usual indication for morphine in most countries, the parenteral route is the most scientific and empirically effective. Recent scientific evaluations of "analgesic cocktails" such as Brompton's mixture indicate that "long tradition" is not necessarily synonymous with scientific fact. One by one the various ingredients of Brompton's mixture seem to be falling by the wayside, despite many years of firm belief in their importance.

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Maintenance of diagnostic equipment in wards and consulting rooms

SIR,—The report of Mr A Shaw and others (24 March, p 789) on errors arising in the use of sphygmomanometers with blocked vents is timely. Other common defects are: (1) dirty graduated tubes causing erratic fall of the mercury column; (2) thinning of the control valve washer causing precipitous fall of the mercury; (3) obstruction of the gauze mesh in the valve by dust resulting in the need for great pressure to squeeze the bulb (very

painful for arthritic fingers); (4) air leaks due to perished rubber tubing.

These faults are easy to identify and their cure can usually be effected in a matter of minutes. The manufacturers of sphygmomanometers might helpfully provide instructions for their identification and correction with each instrument.

This is really part of the wider problem affecting all diagnostic and therapeutic equipment in which faults are just as likely to occur. Clearly all equipment involving moving parts or electrical connections should (like motor cars) be routinely checked and serviced. This would be beyond the capacity of most doctors. At another hospital, where I was formerly on the staff, an attempt was made to set up a system of routine inspection and servicing of ward equipment, but organisational difficulties were encountered and until now no action has been taken.

The time is overdue for the establishment in hospitals of a service for the routine inspection of equipment, for the identification of faults, and for their repair where this is feasible.

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Analgesia in terminal malignant disease

SIR,—The letters by Dr F R Gusterson and others and by Dr I M C Clarke and Miss S M Tempest (7 July, p 47) described clearly some of the advantages of the suppository as a dosage unit for controlling pain in terminal malignant disease. The benefits of using the rectal route for systemic administration apparently are appreciated more widely in continental Europe than in the United Kingdom, if one can judge by the relative numbers of suppository products available. The rate and extent of absorption of suitable drugs from the rectum compare very favourably with the oral route and local adverse effects are rare, other than irritation with certain non-steroidal, anti-inflammatory analgesics.

It is unfortunate, in view of the potential advantages of rectal administration, that there are so few proprietary suppository dose forms containing potent analgesics suitable for the treatment of severe, intractable pain when practitioners without direct access to a hospital pharmacy or dispensary may not be able to obtain readily generic products of this type. The latest copy of *MIMS* indicates that only two proprietary products are available—namely, suppositories of pentazocine lactate and of dextromoramide tartrate. It is our experience that dextromoramide tartrate in Palfium suppositories is rapidly absorbed and well tolerated and that such a dosage form is a useful addition to the normal range of oral and parenteral presentations of potent analgesics.

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Muslims, Ramadan, and diabetes mellitus

SIR,—A Pakistani patient with diabetes mellitus consulted me in a state of agitation. He had heard on a television programme that doctors from a Birmingham diabetic clinic had issued a warning to Muslim diabetics:

"All diabetics don't fast. If you fast you will die." Either he or the TV programme was misquoting the letter of Dr S G Barber and others (7 July, p 46).

Dr Barber and his colleagues write, "Muslims who have diabetes mellitus should be advised not to fast during Ramadan, unless their diabetes is controlled on diet alone." It is difficult to understand why they give this advice, as they show in the first half of their letter that Muslims with diabetes mellitus come to no harm by observing the fast of Ramadan. But they wisely point out that there are theoretical dangers of provoking ketosis by fasting without adequate medical advice.

The patient with diabetes mellitus and obesity who is on a low-calorie diet should find the fast of Ramadan highly beneficial. Those on oral hypoglycaemic agents should take a half or a quarter their usual dose just before sunrise. Those on twice-daily insulin should set their alarm clocks for three quarters of an hour before sunrise. They should have a half or a third of their usual dose of morning insulin, have a meal, and go back to bed. After sunset they should have their usual evening dose of insulin before they break their fast. It might be advisable to change those on a single daily dose of insulin to a twice-daily dose of short-acting insulin for the period of Ramadan. They should ideally be seen weekly during Ramadan and also taught to test for ketones. They should report to their doctor if they have ketonuria or hypoglycaemia.

Dr Barber and his colleagues have produced good evidence that it is quite safe for a Muslim with diabetes mellitus to fast during Ramadan. Helping a patient to practise his set of ideals leads to a good-doctor patient relationship.

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Saving asthmatics

SIR,—We were interested in your leading article "Saving asthmatics" (9 June, p 1520) and the letters following, especially the one from Dr Malcolm Bateson (30 June, p 1791). As he rightly says, there have been a number of studies showing that intravenous salbutamol is an effective bronchodilator in the treatment of acute severe asthma.¹⁻⁴ However, we disagree with his statement that salbutamol is the drug of first choice.

Recently we looked at 21 patients admitted with acute severe asthma. All had a pulse rate of >120 beats/min, a peak expiratory flow rate (PEFR) $<25\%$ of predicted, and a $\text{PaO}_2 < 9.1$ kPa (70 mm/Hg). Each patient was then randomly allocated to one of the following infusion regimens, given initially as a loading dose over 15 minutes, and followed by a lower continuous infusion of the drug for 24 hours. The dosages were on a mg/kg body weight basis as follows (figures for a 70 kg person): (1) aminophylline 20 mg/min for 15 minutes and thereafter 1 mg/min. (2) Salbutamol 20 $\mu\text{g}/\text{min}$ for 15 minutes and thereafter 4 $\mu\text{g}/\text{min}$. (3) A combination of 1 and 2 administered via double outlet infusion pump. Each patient in addition received corticosteroids, potassium supplements, and 35% oxygen via a Ventimask.

Prior to treatment all our groups were similar with respect to pulse, PEFR, and PaO_2 ; but the Paco_2 was significantly higher

in the aminophylline group when compared with the combined group ($P < 0.02$), suggesting more severe asthma in that group.

Our results show that for the aminophylline and combined groups significant bronchodilatation occurred after 15 minutes ($P < 0.005$), while salbutamol had little effect for 45 minutes and significant bronchodilatation did not occur until 60 minutes after the start of the infusion. Mean pulse rates fell with the aminophylline group, remained the same with the salbutamol group, and increased significantly in the combined group. No significant differences were seen in the improvement of PaO_2 between the infusion regimens, although salbutamol was slightly better. We were unable to find a significant synergistic or additive bronchodilator effect when aminophylline and salbutamol were used in combination in acute asthma, unlike stable asthma.⁵

Thus our study confirms the findings of Johnson *et al*¹ that significant bronchodilatation took longer to occur with salbutamol than with aminophylline infusions. The poor bronchodilator response in the salbutamol group and the absence of a drug-induced tachycardia indicate that resistance to beta-stimulation may occur, suggesting that Sventivanyi's theory of beta-blockade in acute asthma may be correct.⁶ Endogenous sympathetic drive in acute attacks may already be maximally stimulating the bronchial adenylyl cyclase system, and further bronchodilatation would be unlikely unless cyclic adenosine monophosphate levels could be increased in other ways—for example, by preventing its breakdown. Aminophylline, by inhibiting phosphodiesterases, could be expected to do just this; and providing it is administered slowly, especially the loading dose, we feel that it remains the bronchodilator of choice in the treatment of acute severe asthma.

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¹ Fitchett, D H, *et al*, *British Medical Journal*, 1975, **1**, 53.

² Williams, S J, *et al*, *British Medical Journal*, 1975, **4**, 685.

³ Ferni-Pearce, D, *et al*, *British Medical Journal*, 1977, **1**, 491.

⁴ Johnson, A J, *et al*, *British Medical Journal*, 1978, **1**, 1013.

⁵ Campbell, I A, *et al*, *Thorax*, 1977, **32**, 424.

⁶ Sventivanyi, A, *Journal of Allergy*, 1968, **42**, 203.

Asthma due to industrial use of chloramine

SIR,—I was interested to read the article by Dr M S Bourne and others (7 July, p 10) on asthma due to chloramine. I would like to describe a further case in which laboratory and occupational challenges were performed and the bronchospasm was found to be of delayed onset.

A 43-year-old ex-smoker complained of cough, wheeze, and excessive sneezing for nine months. He had worked at a brewery for three years and his main task was disinfecting beer tanks with an aerosol of chloramine solution. A challenge to chloramine was performed in a lung function laboratory. Forced expiratory volume in one second, vital capacity, and peak expiratory flow rate were measured. The patient was instructed

to dissolve a quantity of fine chloramine powder in water and pour the solution from one container to another for four minutes. There were no symptoms and no alterations in lung function following this. After a period away from work he returned to the brewery. Peak respiratory flow rate (PEFR) was measured and he proceeded to dissolve chloramine in water and spray one of the beer tanks with chloramine solution. He wore the mask supplied for this task. There were no immediate symptoms; nor was there a reduction in PEFR. Seven hours later there was a 62% fall in PEFR accompanied by chest tightness, wheeze, and cough.

He was advised to leave the brewery, but was reluctant to do so. The company were unable to move him to another job away from chloramine. He was started on inhaled salbutamol and beclomethasone and was able to return to work without any further symptoms and without any deterioration in his lung function.

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Glycosylated haemoglobin and hyperglycaemia

SIR,—We read with interest the article by Dr R D G Leslie and others (7 July, p 19) describing rapid increases in glycosylated haemoglobin (HbA_1) which were attributed to recent short periods of increased hyperglycaemia. We would confirm from our experience that many insulin-requiring diabetics do show significant changes in HbA_1 (up to 5%) over periods as short as one to two weeks, but would suggest that the duration of hyperglycaemia necessary to produce a rise in HbA_1 may be much longer than indicated in their paper.

Unless blood glucose levels are monitored continuously over several weeks, short periods of hyperglycaemia may be undetected, and the cumulative effect of these will be to cause the HbA_1 to rise one to two months later. Thus an increase in HbA_1 one week after an elevation of blood glucose may in fact be reflecting changes in blood glucose that occurred several weeks earlier, and might well have been missed by routine urine testing or random blood glucose estimation at a clinic visit.

We agree, however, with Dr Leslie that a single HbA_1 measurement may not truly reflect the quality of blood glucose control because of the rapid changes that may occur, and we would suggest that it is the trend in serial HbA_1 measurements that is more helpful in assessing diabetic control than the traditional random blood glucose estimation.

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Fifty years of penicillin

SIR,—Sir George Pickering and Dr V D Allison suggest (16 June, p 1625) that Sir Almroth Wright's attitude discouraged Fleming from pursuing attempts to isolate penicillin as a therapeutic agent. Perhaps so, but it is on record nevertheless that Fleming was not unduly inhibited about promoting penicillin. He characterised it, correctly, as being soluble