"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

in water and ethanol, insoluble in chloroform and ether, stable at pH 6.8, and moderately stable to heat.¹ He also consulted a number of colleagues in 1929 and subsequently about how to proceed with extraction. Two of them, Stuart Craddock and Frederick Ridley, evaporated extracts in vacuo without success. Fleming then consulted several chemists independently, including Harold King, head of the Medical Research Council's laboratory at Hampstead, who told me later that they "had not been able to do much work on penicillin." Harold Raistrick, professor of biochemistry at the London School of Hygiene, worked harder on the problem collaboratively with R Lovell and P W Clutterbuck, but they were equally unsuccessful.² I have in my possession a bottle of dried yellow pigment purified by Raistrick from the crude brew in 1930 and given to me later by one of his assistants. When tested many years ago it contained none of the stable degradation products of penicillin. From 1932 onward, there are no records of further attempts to extract any active principles from the penicillin mould or the crude brew.

In retrospect, it is very surprising that bacteriologists of the time ignored his findings, for filtrates of crude brew killed staphylococci and other organisms at dilutions of 1600, were non-toxic to leucocytes, and apparently eliminated sensitive organisms from burns, wounds, and ocular and other localised infections.³ Until 1936 Fleming continued to draw attention to these unique properties but no one in the domestic research councils or pharmaceutical industry, or internationally, evinced any interest.⁴ My reading of the record⁵ and my acquaintance (later) with Fleming himself leave me convinced that he did not surrender easily to Wright or anyone else, but that he was by 1936 at his wit's end. So he followed the only course open to an honest scientist by describing his findings in a manner which left open the track, accurately, for the subsequent discovery of the active principle at Oxford a few years later by Chain, Florey, and their colleagues.

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¹ Fleming, A, *British Journal of Experimental Pathology*, 1929, 10, 226.

² Clutterbuck, P W, Lovell, R, and Raistrick, H, *Biochemical Journal*, 1932, 26, 1907.

³ Wright, A D, *The Medical Society's Transactions*, 1945, 64, 142.

⁴ Fleming, A, in *Proceedings of Second International Congress of Microbiology*, ed R St John Brooks, p 33. London, International Society for Microbiology, 1937.

⁵ Stewart, G T, *The Penicillin Group of Drugs*, Amsterdam, Elsevier, 1965.

Easy-rider sling

SIR,—For generations Africans, American Indians, and Australian Aborigines have carried their children close to them, mostly strapped to their backs. This technique of portage has been imported into the "developed" countries and the advantages in total mothering is obvious. I wish, however, to express some concern about this and to draw attention to a hazard of carrying babies in the front.

A 5-week-old child was brought to the accident and emergency department having been involved in a fall. She was being carried in a sling worn in front when her mother

tripped and fell on her face. On examination she had a large haematoma on the right side of the head and skull x-ray film showed a fracture on the right parietal bone. Skeletal survey revealed no other fractures. This is a particularly interesting case for a number of reasons. It made us aware of another differential diagnosis in non-accidental injury. The mother of this child was under treatment for postnatal depression. Our liaison health visitor recalled three other similar incidents when mothers had tripped and fallen forwards.

Most important is the dynamics of falling: it is rare to fall backwards from a trip. It is more usual to fall forwards, thereby involving a baby in the process. It will be interesting to know if any of your readers have been presented with similar problems. Should it not be possible for manufacturers of slings to state warnings and possible dangers?

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Compliance with drug treatment

SIR,—We were interested in the papers on drug compliance by Dr D A Ellis and others (17 February, p 456) and Dr A Smith and others (19 May, p 1335). Many elderly patients and some who are not so elderly have difficulties in remembering the exact daily dosage when they are on more than one drug. We have found it useful to give such patients a card to which is fixed by Sellotape an example of each tablet which the patient is taking with written instructions beside the tablet. We find that this simple step helps greatly to avoid confusion about dosage.

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Prophylaxis of tetanus

SIR,—Dr J F Stent (7 July, p 50) could not be more correct. For a non-immunised patient with a tetanus-prone wound neither tetanus toxoid nor antibiotics either together or singly provide necessary prophylaxis against tetanus intoxication.

The advocacy of such prophylaxis stems from the highly immunised and oversensitised communities of the West, among whom there may be more fatalities from the careless administration of antitetanus serum (ATS) than from tetanus. Nevertheless, the fact remains that one cannot rely on toxoid with or without antibiotics for a contaminated wound in someone whose previous immunisation is in doubt. The circumstantial evidence given by Dr Stent can be repeated many times.

Over some years in our north India rural 200-bed hospital where 10% of village-born babies develop tetanus and 1% of admissions are for tetanus, some 7000 severely contaminated wounds (late burns, compound fractures, tiger mauls, etc) had routine 500 units or 750 units prophylactic ATS and not one developed tetanus. At a hospital I knew, however, the specialist paediatrician, flushed with "recent advances" and without consultation, forbade the routine ATS and relied on only toxoid with penicillin. Two of the first three

(and last) children so treated developed tetanus and one died. For India's widespread vasectomy campaigns (at least up to 1975) Western advice prevailed in the instruction to give only toxoid and procaine penicillin at the time of operation. The resulting incidence of postoperative tetanus was sometimes as high as 1%. At the same time Indian surgeons in some big city hospitals insist on prophylactic ATS for their private patients.

I am convinced we need use only very small amounts of ATS prophylactically, certainly not more than 500 units and probably less than 100 units. One unit of ATS is capable of neutralising six minimal lethal doses to a 60 kg man. The question is, therefore, not how much ATS to use but how little and where and when. This also applies to the therapeutic use of ATS, where, as with the non-immunised tetanus prone wound, ATS should not be omitted (7 July, p 49).

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Oral metronidazole in *Clostridium difficile* colitis

SIR,—We were interested in the report by Mr N L Pashby and others (16 June, p 1605), describing two cases of *Clostridium difficile* colitis treated with oral metronidazole. Two of our cases cast doubt on the value of metronidazole for treatment of this condition. The first patient was given oral metronidazole for 11 days, during which time the faecal toxin titre did not fall. The second patient acquired *Cl. difficile* and developed a low titre of faecal toxin while receiving metronidazole. He had also been given neomycin and metronidazole preoperative bowel preparation, and co-trimoxazole, gentamicin, and nitrofurantoin before the onset of colitis.

We believe that vancomycin should remain the treatment of choice in severe cases of colitis due to *Cl. difficile*. Contrary to the statement made, vancomycin is not toxic when given orally, because it is not absorbed. An oral preparation consisting of coarse powder is available, which can be taken as a suspension in fruit juice. It is not necessary to use the parenteral preparation for oral therapy. Although vancomycin is expensive, we have found that a dose of only 125 mg four times daily achieves satisfactory levels in the colon.

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Mission hospital medicine

SIR,—I heartily agree with the sentiments and proposals clearly stated by Dr Anne Savage (14 July, p 111). As one of the several Glasgow clinicians who participated in a scheme to set up a medical school in Nairobi in the 1960s I can confirm the undoubted benefits to trainees—not only in widening their horizons in general, but equally in greatly extending their operative skills. There is no doubt that from the practical point of view a BTAf degree is far superior to BTA (been to America), and what are surgeons if they are not practical?

With the present rat race I know it is risky