justifiably concerned that her baby was convulsing in utero. It was subsequently noticed that her baby was frequently affected by hiccups following a feed. The hiccups occurred at a rate of one per second and lasted for several minutes at a time; this phenomenon persisted to the age of three months.

It is known that the fetus drinks liquor in utero, and hiccups have been demonstrated by real-time ultrasound scanning.¹ Hiccupping in utero might explain the observations of these mothers and such an explanation by her doctor would help to allay genuine anxieties.

Real-time scanning would be valuable to confirm this diagnosis when the technique is available.

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¹ Roberts, A B, *Midwife, Health Visitor, and Community Nurse*, 1978, **14**, 256.

Infant-feeding practices among immigrants in Glasgow

SIR,—Rickets among Asian children in Glasgow has been recognised as a serious problem for 15-20 years¹ and in their recent paper Dr K M Goel and others (28 October, p 1181) restate their earlier finding that 12.5% of Asian children in their sample had the disease. Such a high prevalence would appear inconsistent with an absence of their findings, that a high proportion (87%) of their Asian children received vitamin preparations. It is not clear, however, whether the taking of vitamin preparations necessarily includes vitamin D and also whether it refers to an adequate course, sufficient to protect against the disease throughout childhood, or merely to vitamins having been taken at some time. The fact that many Asian children still present clinically with acute rickets at Glasgow hospitals provides corroborative evidence for a continuing high prevalence of the disease and suggests that overall vitamin supplementation is grossly inadequate.

It is all too easy to believe that because a problem has been recognised for a long time and is readily preventable and measures have been previously instituted it must have been solved. There should be no such deception or complacency in the case of rickets. Prevention in Asian children is a community problem which requires a renewed and sustained initiative from the health, educational, and social services professionals acting jointly with the parents and leaders of the Asian community.

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¹ Dunnigan, M G, *et al*, *Scottish Medical Journal*, 1962, **7**, 159.

Inadequacy of information on side effects

SIR,—The letter from Drs H C Drysdale and M D Hellier (7 October p 1021) highlights a problem which faces all who attempt to provide information about the adverse effects of drugs: what should be included?

The description of adverse effects in a drug's data sheet has to serve two purposes: it should indicate those effects which have been attributed to the drug and it should give the prescriber some idea of the potential toxicity of the drug. A comprehensive list of all reported adverse effects may not be the most useful way of indicating to the prescriber what he should anticipate when using the drug. Furthermore, the medical literature is full of reports of adverse drug reactions which are poorly documented and in which the causal relationship is far from established. It is important that these should not become part of the "toxicity profile" of the drug solely on the basis of such reports.

A possible way of dealing with the problem would be to classify the adverse effects of a drug into three groups. Group 1 would be those side effects which appear to be dose-related and occur fairly predictably in a proportion of patients treated; for many of these effects it is possible to give a rough guide to how often they occur from clinical trials data. Group 2 would contain reactions which are less common but well documented and reported frequently enough for a causal relationship to be accepted. Group 3 would contain reactions which, although reported in the medical literature, have not been adequately documented and for which a causal relationship remains to be established.

From Group 1 the prescriber could obtain a rough idea of what adverse effects to anticipate when using the drug. Groups 2 and 3 he could use to help him decide whether a reaction occurring in a particular patient was likely to be due to that drug. It would be especially important to document fully any reactions described under Group 3 and to make sure that they were reported not only to the Committee on Safety of Medicines but also to the drug company concerned.

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Disentangling Kaposi's sarcoma

SIR,—Your leading article (14 October, p 1044) refers to some of the problems that are peculiar to this tumour. You state that "the endemic occurrence of an unusual neoplasm in malarial areas parallels Burkitt's lymphoma," and it has been suggested that this association might be due to the known immunosuppressive effect of malaria which may play a role in the aetiology of Burkitt's lymphoma. The distribution and clinical features of Kaposi's sarcoma have recently been reviewed in a series of papers from Malawi,¹ Uganda,² Tanzania,³ and Zambia.⁴ There is no evidence to suggest that the tumour is related to the endemicity of malaria or to any other specific parasitic disease. For example, in Tanzania the regions of lowest incidence of Kaposi's sarcoma are among the regions of highest malaria transmission. Moreover, in Uganda Kaposi's sarcoma is often seen in the mountainous, malaria-free south-west, where Burkitt's lymphoma does not occur. Unfortunately there is as yet no adequate explanation for the very large local variations in incidence in east and central Africa and, in particular, for the very high rates in western Uganda and eastern Zaire.

The sex distribution of the tumour in Africa is also difficult to explain. In children under the age of 15 the male:female ratio in three of these reports was less than 2.5:1, but there was an increasing ratio over this age, reaching 8:1-14:1 at over 40 years. It is difficult to believe that this could be due to different exposure to an environmental influence in these rural areas, although the overall geographical distribution suggests an environmental agent. It seems more likely that endogenous, possibly hormonal, factors play an increasing role with age in determining susceptibility or resistance to the causative agents.

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¹ O'Connell, K M, Borgstein, J, and Hutt, M S R, *East African Journal of Medical Research*, 1977, **4**, 59.

² Owor, R, and Hutt, M S R, *East African Journal of Medical Research*, 1977, **4**, 55.

³ Bland, J M, Mutoka, C, and Hutt, M S R, *East African Journal of Medical Research*, 1977, **4**, 47.

⁴ Naik, D G, *East African Journal of Medical Research*, 1977, **4**, 65.

Body weight and endocrine function in anorexia nervosa

SIR,—We were glad to read that the findings of Dr A Wakeling and his colleagues on endocrine function in anorexia nervosa (21 October, p 1164) are in agreement with our own (19 August, p 526) and look forward to seeing the published data. In our study the initial test was carried out as soon as possible after admission in most cases, as we wished to investigate the patients in the untreated state. Clearly the minor impairment in prolactin secretion which we demonstrated (20 August 1977, p 521) is readily reversible on refeeding, and Dr Wakeling's work appears to show that this requires as little as five days' dietary treatment. Our own observations on patients tested during the course of weight gain are in accordance with this.

With regard to the hypothesis of excessive central dopaminergic activity in anorexia nervosa, we have merely stated that this would be consistent with our findings of diminished prolactin and thyrotrophin (TSH) reserve, whereas the alternative hypothesis of dopamine depletion would be inconsistent. No implication as to the aetiology of the disease is intended. Even proved dopamine excess might well be secondary to starvation, as are so many of the other clinical, endocrine, and biochemical features of anorexia nervosa.

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Somalis with iron deficiency

SIR,—The paper by Professor M J Murray and others (21 October, p 1113) is an interesting contribution to the discussion of the interaction of iron deficiency and infection. Their findings should be noted by those who

provide medical care for nomadic pastoralists. They state, however, that among the Somalis iron deficiency is rarely fatal. This is not true in the North-eastern Province of Kenya, where 250 000 Somalis live. In 1974 Bonte¹ pointed out that the North-eastern Province was unique among the provinces of Kenya in that blood diseases came top of the causes of death in hospital. Severe anaemia is the commonest single cause for hospital admission in the provincial and district hospitals.

Community studies have shown the high prevalence of anaemia.² Of 787 Somalis living in the bush, 190 (24%) had haemoglobin levels less than 8 g/dl and 33 (4%) values below 5 g/dl. Many of these people continue their daily activities with no symptoms, but their reserve is small. In the event of injury, childbirth, or acute malaria (all common events) the value may fall to 2 or 3 g/dl very suddenly. They then die or, if fortunate, survive a journey of 100 miles (160 km) to arrive in hospital with severe heart failure.

Professor Murray and his colleagues suggest that it may be unwise to correct iron deficiency in the face of quiescent infection. It is true that tuberculosis is a major problem and that brucellosis is common. The possible risks of reactivating infection, however, must be weighed against the at least equally serious risk of ignoring severe anaemia. The note of caution is an invitation to nihilism. Those who are building up services for Somali nomads will turn their attention to the anaemia and the pellagra and xerophthalmia which also result from the all-milk diet. They will also turn their attention to the infectious diseases. For a professor of medicine to arrive in a refugee camp of 6000 people bringing the facility for laboratory investigations but only 7000 iron tablets is only comparable to a Lord of the Admiralty reaching the sinking *Titanic* equipped with radar but in a four-seater rowing boat.

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¹ Bonte, J, in *Health and Disease in Kenya*, ed L C Vogel, et al, pp 75-90, Nairobi, East African Literature Bureau, 1974.

² Greenham, R, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1978, **72**, 72.

Rethinking antenatal care

SIR,—I am sure that I was not the only reader whose eye was caught by the title of your leading article (28 October, p 1177) only to be disappointed by its wholly technical content. As it correctly pointed out, there is as yet no satisfactory explanation for the inverse relationship between numbers of antenatal clinic visits and peri- and neonatal morbidity and mortality rates. However, unless and until a causal association is definitely disproved practitioners and health authorities have a responsibility to do everything possible to encourage early and continued attendance at antenatal clinics.

The Department of Health has laudably acknowledged this responsibility, and has recently published the highly informative proceedings of a conference it held around this topic in conjunction with the Child Poverty Action Group in April of this year.¹

The characteristics of late attenders have been well known for some time^{2,3} and there is much that can be done to reach them within

existing resources—for example, improvement of communication between general practitioners and obstetricians,⁴ reorganisation of antenatal clinics, redeployment of community midwives,⁵ and health education initiatives specifically aimed at the women concerned, such as the youngest primigravidae. Elsewhere you have recently demonstrated your awareness of the importance of the expectations of the patient,⁶ and it is now time for the profession to follow in rethinking not only the content but also the style of antenatal care.

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¹ Department of Health and Social Security/Child Poverty Action Group, *Reaching the Consumer in the Antenatal and Child Health Services* (issued with Health Notice HN(78) 108). London, DHSS, 1978.

² McKinlay, J B, *British Journal of Preventive and Social Medicine*, 1970, **24**, 52.

³ Robertson, J S, and Carr, G, in *In the Beginning*. London, Nuffield Provincial Hospitals Trust, 1970.

⁴ Heward, J A, and Clarke, M, *British Medical Journal*, 1976, **1**, 1202.

⁵ Willmott, J A D, *Midwives Chronicle and Nursing Notes*, 1976, **89**, 236.

⁶ *British Medical Journal*, 1978, **2**, 188.

Smoking and deep-vein thrombosis

SIR,—Mr J K Clayton and others (5 August, p 402) have presented convincing evidence of the "protection" of cigarette smokers against postoperative deep-vein thrombosis and the increased risk associated with overweight for height. They conclude that the explanation for the "protection" of smoking patients provided they are lean remains obscure.

It seems fair to suggest that the "apparent" protection of smoking was due to the "real" protection of lean body habitus, known to be associated with smoking, and was unrelated to smoking per se.

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Postoperative pain

SIR,—We welcome your excellent leading article on this subject (19 August, p 517) because this neglected area of therapeutics has concerned us for some time. Despite the ready availability of potent analgesic drugs patients still rank postoperative pain high on their list of unpleasant perioperative memories. This is not surprising, because very little is known about the relationship between the pharmacokinetics and pharmacodynamics of even the oldest agents.¹

Using pethidine as a model, we investigated the hypothesis that poor analgesia was due simply to inadequate and variable blood concentrations of the analgesic drugs.² We found a direct relationship between blood pethidine concentration and analgesic effect. The minimum therapeutic concentration for postoperative pain was found to be 0.45-0.55 mg/l. This is more than double the value previously reported after a single injection³ administered immediately after emergence from general anaesthesia. Repeated (4-7) intramuscular injections of pethidine resulted in fluctuating and often inadequate blood pethidine concentrations. Peak pethidine concentrations varied fivefold among patients and

twofold within patients. The time to reach peak concentrations varied by a factor of 8 among patients and by a factor of 2 within patients. Blood pethidine concentrations fluctuated markedly above and below the minimum therapeutic level and this was reflected in the analgesic response. Time above the minimum therapeutic concentration varied from 0 to 100% (mean $\pm$ SD = $35 \pm 36\%$) for the four-hour period after each injection.

However, in a subsequent study it was shown that only a twofold difference in clearance occurred among patients,^{4,5} suggesting that variation in absorption from the intramuscular site is the major reason for poor analgesia. Using a pharmacokinetic simulation system, an intravenous infusion regimen was designed to avoid the variability in absorption rate and to provide stable therapeutic blood concentrations.⁴ Controlled continuous intravenous infusion of pethidine produced stable blood concentrations which were maintained above the therapeutic level for postoperative pain and provided excellent pain control. Severe pain was not experienced by any person after three hours and analgesia continued for the duration of the two-day study. The continuous intravenous infusion technique has been successfully used in intensive care for up to 10 days and is currently being evaluated for other uses.

We conclude that (1) pethidine has a therapeutic blood concentration of 0.45-0.55 mg/l for pain following abdominal surgery; (2) variable response to intramuscular injection results from inadequate and fluctuating blood concentrations; (3) the intramuscular route of administration alone is the major cause of the variability in response; and (4) controlled intravenous infusion of pethidine provides continuous analgesia and may offer a significant advance in pain management.

The plethora of new parenteral agents which the pharmaceutical companies have introduced over the past 20 years is not a reminder that we have not found the right drug but a reminder that we had not found the optimal mode of administration of perfectly adequate analgesic drugs.

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¹ Mather, L E, et al, *British Journal of Anaesthesia*, 1975, **47**, 1269.

² Austin, K L, Stapleton, J V, and Mather, L E, Meeting of Australasian Society of Clinical and Experimental Pharmacologists, Melbourne, 1978, abstract No 18. (Paper in preparation.)

³ Shih, A P L, Robinson, K, and Au, W Y W, *European Journal of Clinical Pharmacology*, 1976, **9**, 451.

⁴ Stapleton, J V, Austin, K L, and Mather, L E, *Anaesthesia and Intensive Care*. In press.

⁵ Mather, L E, Austin, K L, and Stapleton, J V, Meeting of Australasian Society of Clinical and Experimental Pharmacologists, Melbourne, 1978, abstract No 19.

Crohn's disease—40 years on

SIR,—I was interested in your leading article (21 October, p 1106) and wish to make some further comments. As you suggest, crude recurrence rates are meaningless and they must be related to time.¹ Even then some interesting points may be missed. Although it is now agreed that related to time the recurrence rate for ileal disease is higher after a