general condition improved rapidly from that time. However, the oedema continued to extend across his chest wall and his left arm and, more worryingly, up into his neck; and at one point we began to consider the possibility that tracheostomy would be required. Happily this did not prove necessary, but it was not until 4 August that the oedema began to recede, and on 13 August when the boy was discharged from hospital supervision there was still some residual swelling of his right arm.

It seems likely, since this boy arrived in the hospital 45 minutes after the bite, that antivenom given at that stage would have prevented much of his very worrying illness. I would therefore make a plea for the updating of official policy on the use of antivenom, as suggested by Dr Reid.²

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¹ Walker, C W, *British Medical Journal*, 1945, 2, 13.

² Reid, H A, *British Medical Journal*, 1976, 2, 153.

Vasodilators in senile dementia

SIR,—The *BMJ* has a world-wide reputation for balanced and accurate reporting and informed editorial comment. Your leading article "Vasodilators in senile dementia" (1 September, p 511) is, however, misinformed with regard to dihydroergotoxine mesylate (co-dergocrine mesylate—Hydergine).

You state that vascular (or multi-infarct) dementia is the condition for which drug manufacturers recommend cerebral vasodilators. This is inaccurate as regards co-dergocrine, for which the indication is symptoms of senile dementia presenting as mild-to-moderate impairment of mental function in the elderly.¹

Co-dergocrine is an alpha-blocker, but its mechanism of action is not solely dependent on this property.¹ In addition to the α -adrenoceptor-blocking properties inhibiting the rate of breakdown of cellular ATP, animal studies show that co-dergocrine mesylate also inhibits the enzyme cAMP-phosphodiesterase reducing the breakdown of cellular cAMP and improving the energy balance of the cell²; while more recently it has been shown to have dopaminergic and serotonergic properties,⁴ which may help to explain its effects on symptoms of senile dementia, the cause of which may be due to an impairment in one or more neurotransmitter pathways.

Work in Glasgow⁵ has indicated a broad relationship between slowing of the basic frequency of the EEG and the severity of mental impairment in both vascular and non-vascular dementia. A three-month study⁶ in geriatric patients showed that the improvement induced by co-dergocrine in age-related changes in the EEG was accompanied by clinical improvement in patients with similarly age-related mental deterioration.

Despite the critical review⁷ quoted in your article the evidence was accepted by the US Food and Drug Administration as proof of efficacy, and the same review concluded that "future studies with better methodology and design may lead to more favourable conclusions." Further studies have taken place,^{8,10,13} and a more recent review,⁹ which you also quote, states, "All of these trials note significant improvement of dihydroergotoxine-treated patients on some behavioural or psychological measure; in 18, improvement is considered to be of practical importance. Overall, this drug has the best confirmed efficacy, a result

consonant with a recent quantitative analysis of 12 of these studies."

The reference to sinus bradycardia and hypotension as side effects in the critical review of clinical trials is misleading. One clinician and his colleagues reported sinus bradycardia in an open study involving three out of eight patients,¹⁰ but another reported no such occurrence in a series of 40 patients.¹¹ The incidence of hypotension is small. A controlled long-term study of 100 patients over a period of 15 months reported no side effects,¹² and further data collected from 25 studies on 1593 elderly patients gave an incidence of any form of dizziness or hypotension of 1.82%.¹³

The statement that this ergot compound may lead to vascular insufficiency and gangrene is a serious allegation and must be corrected. Nickerson and Collier¹⁴ state that the prolonged administration "of any of the natural peptide ergot alkaloids can cause vascular insufficiency and gangrene," but co-dergocrine is not a natural peptide. In fact Nickerson and Collier state that "its [co-dergocrine's] overall effects include peripheral vasodilation and a fall in arterial blood pressure." Furthermore, co-dergocrine given intravenously or intra-arterially induces an increase in blood flow in hand and foot.¹⁵

Co-dergocrine mesylate has been available in this country since 1950 and no cases of gangrene have been reported. In fact, though the drug has been used extensively throughout the world for many years, only seven cases of cyanosis of the extremities or gangrene have been reported in the last 10 years, and in none of these was the condition proved to be definitely associated with the drug.

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¹ Manufacturers' Data Sheet, 1979.

² Hyams, D E, in *Textbook of Geriatric Medicine and Gerontology*, ed J C Brocklehurst, 2nd edn. Edinburgh, Churchill Livingstone, 1978.

³ Meier-Ruge, W, and Iwagoff, P, *Postgraduate Medical Journal*, 1976, 52, suppl No 1, p 47.

⁴ Loew, D M, Vigouret, J M, and Jaton, A L, *Postgraduate Medical Journal*, 1976, 52, suppl No 1, p 40.

⁵ Roberts, M A, McGeorge, A P, and Caird, F I, *Journal of Neurology, Neurosurgery, and Psychiatry*, 1978, 41, 903.

⁶ Matejcek, M, et al, *Journal of the American Geriatrics Society*, 1979, 27, 178.

⁷ Hughes, J R, Williams, J G, and Currier, R D, *Journal of the American Geriatrics Society*, 1976, 24, 490.

⁸ Shader, R I, Harmatz, J S, and Salzman, C, *Journal of the American Geriatrics Society*, 1974, 22, 107.

⁹ Yesavage, J A, et al, *Archives of General Psychiatry*, 1979, 36, 220.

¹⁰ Cayley, A C D, MacPherson, A, and Wedgwood, J, *British Medical Journal*, 1975, 4, 384.

¹¹ Cohen, C, *British Medical Journal*, 1975, 4, 581.

¹² Kugler, J, et al, *Deutsche medizinische Wochenschrift*, 1978, 103, 456.

¹³ Sandoz Information Document, 1979.

¹⁴ Nickerson, M, and Collier, B, in *The Pharmacological Basis of Therapeutics*, ed L S Goodman and A Gillman, p 540. New York, Macmillan, 1975.

¹⁵ Clark, B J, Chu, D, and Aellig, W H, *Ergot Alkaloids and Related Compounds*, ed B Berde and H O Schild, p 355. Berlin, Springer-Verlag, 1978.

SIR,—Your leading article on vasodilators in senile dementia (1 September, p 511) comments on the treatment of vascular dementia with, among other drugs, vasodilators. Specifically, isoxsuprine, a β -adrenergic stimulant, is indicated as being without value and indeed possibly even causing a reduction of cerebral blood flow owing to a "steal" effect. Unfortunately these claims are not substantiated by any references.

This view is not shared by others; for example, Ussher¹ commented that cerebrovascular dilators like isoxsuprine (Duvadilan)

and cyclandelate (Cyclospasmol) may slow down the process of arteriosclerotic dementia if taken both regularly and at an early stage in the process. Furthermore, Hussain *et al*² in a double-blind controlled study of isoxsuprine against placebo found a significant difference in improvement of mental performance between treated and untreated groups, the treated group having a significantly better score ($P=0.047$, two-tailed tests). This study serves to confirm earlier work carried out by Dhrymotis and Whittier.³

The question of "steal" effect is more difficult to confirm by clinical studies and indeed this very point was made in a previous leading article in the *BMJ*⁴ which indicated that the effect was unproved. However, Horton and Johnson,⁵ who carried out double-blind radioisotope studies with isoxsuprine, concluded that both cerebral blood volume and blood flow were increased. Other experiments⁶ with cerebral angiographs have also demonstrated improved blood flow through the brain in patients taking isoxsuprine after the effect of the contrast medium has been eliminated.

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¹ Ussher, C W J, *Modern Geriatrics*, 1977, 22, 11.

² Hussain, S M A, et al, *Practitioner*, 1976, 216, 222.

³ Dhrymotis, A D, and Whittier, J R, *Current Therapeutic Research*, 1962, 4, 124.

⁴ *British Medical Journal*, 1977, 1, 1.

⁵ Horton, G E, and Johnson, P C, *Angiology*, 1964, 15, 70.

⁶ Gloning, K, and Klausberger, E M, *Wiener Klinische Wochenschrift*, 1958, 70, 145.

* * A recent review of clinical trials of vasodilators in senile dementia has found that there have been only five studies of isoxsuprine since 1958.¹ Of these, three meet all the criteria of well-conducted trials. None of these three have shown isoxsuprine to be practically useful, although some improvement in cognitive function was reported in two studies. One study of intravenous isoxsuprine showed that it produced a reduction in cerebral blood flow in most of the patients who were studied.² More persuasive data are needed before isoxsuprine can be recommended for patients with vascular dementia.—ED, *BMJ*.

¹ Yesavage, J A, et al, *Archives of General Psychiatry*, 1979, 36, 220.

² Fazekas, J F, and Alman, R W, *American Journal of the Medical Sciences*, 1964, 248, 16.

Current trends in contraception

SIR,—The report by Mr I D Nuttall and others (15 September, p 641) concerning the changes in choice of contraceptive method by women in the Palatine Centre family planning clinic over a period of four years was most interesting. However, the implication that the primary reason for change from pill use to other methods, particularly the intrauterine contraceptive device, was the reaction of patients to adverse publicity concerning pill use and thromboembolic disease leaves out one quite important variable: the physicians who staffed the family planning clinic and their attitudes toward various methods of contraception.

It is my experience that physicians, be they obstetrician-gynaecologists or general practitioners, have a great deal to do with the ultimate choice of contraceptive methods by their patients. Irresponsible and often incomplete reporting of the medical literature

in the lay press can be a source of misinformation which might lead women to change methods of contraception or to select a different initial method. However, the reading and interpretation of this same medical literature by physicians and its effect on their discussion of various methods with patients has perhaps a more profound impact on choice.

Women come to the consultation with many questions and ask their doctor to interpret what often appears to be conflicting information on contraceptive methods. By not elaborating on the changing attitudes of the doctors who were doing the family planning in the Palatine family planning clinic, the authors sought to explain the decrease in the choice of the pill over the four-year period by the influence of the media on the public rather than by the influence of the changing in attitude of the doctors as these changes affected the consultation. The power of the doctor in the doctor-patient relationship to influence choice is well known and should not be ignored when attempting to analyse changes in patients' behaviour.

The differences in contraceptive choice between the authors' data and the American study they cite may reflect prevailing biases and attitudes of the doctors more than the patients. Controlled studies taking into consideration physicians' attitudes toward various contraceptive methods as well as other issues, such as physicians' feelings about abortion as an alternative to contraceptive failure, should be carried out if a true picture of the reasons for the changing pattern of contraceptive choice is desired.

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Sternal puncture

SIR,—In his paper, Dr Clifford Hawkins (15 September, p 638) points out the anxiety and physical discomfort caused by, among other investigations, sternal puncture, and mentions that fear of needles is very common among patients and that even the sight of someone approaching with a syringe causes alarm.

I am sure that his patients would find that the posterior iliac crest is a better site for marrow biopsy. Though biopsy is technically slightly more difficult at this site, it is much less painful, potentially less dangerous, and yields a better specimen—and the patient can see little of what is being done.

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Babesiosis in man

SIR,—We read with interest the case report by Dr J H Entrican and others on babesiosis in man (25 August, p 474). They are, however, incorrect to state that this is the first recorded case of this infection in the United Kingdom. A patient infected by *Babesia divergens* was reported from Northern Ireland in 1968,¹ and described more fully the following year.²

Our patient had also had a splenectomy and presented with massive intravascular haemolysis and renal failure. There was strong evidence that he acquired his infection while on a caravan holiday, cases of redwater fever

in cattle being reported from that area during the same month. At that time there had been only two previously recorded cases of this infection in man.

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¹ Fitzpatrick, J E P, *et al*, *Nature*, 1968, **217**, 861.

² Fitzpatrick, J E P, *et al*, *British Medical Journal*, 1969, **4**, 770.

Unwanted journals

SIR,—As a principal newly arrived in general practice from vocational training I receive the following free: *Update, General Practitioner, Medicopost, Medicine, Pulse, Hospital Doctor, On Call, Medical News, World Medicine, and Prescribers' Journal*. Several of these carry a common computer number and have jointly located my new home. Since like most mortals I live 24-hour days in which there are certain other functions to fulfil, I choose to read only three of these, plus chosen subscription journals. The rest I jettison unread.

The costs of scarce raw paper, printing, packaging, and distribution must be borne by the advertisement revenue, presumably out of profits on pharmaceuticals. However, the less definable costs of further burdening the Post Office and of waste disposal are borne by all of us. We doctors also have the nuisance of sorting wheat from chaff. Worse, the Great Unwanted ignore my repeated requests for cancellation. How can we curtail this flood of unrequested mail, brought on us by our prescribing power? Does anyone agree that this is urgent, or is this another One Lone Voice Protesting Subject (OLVPS), like that of the admirable Dr D H Judson (8 September, p 613)?

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Post-marketing surveillance of drugs

SIR,—Your readers might infer from Professor D H Lawson's letter (1 September, p 546) in response to our paper on the methodology of monitored release (21 July, p 163) that the terms "monitored release" and "post-marketing surveillance" are synonymous. We would like to point out that the methodology described by us was quite different from that suggested by Professor Lawson.^{1 2}

Professor Lawson criticises us for concluding "that post-marketing surveillance studies are unlikely to add much to the knowledge and understanding of new drugs already gained from preregistration clinical trials." But in fact the conclusion in the paper related specifically to monitored release of buprenorphine and not to post-marketing surveillance in general.

We defend our statement that "monitored release, however large the cohort size, without a suitable (randomised?) control group, is a methodological impasse when rare events are considered." Professor Lawson's observations on this statement refer to *common serious events* with an incidence of one in 500, and not to rare events. If an effect has not been seen in 1921 patients the true incidence is less

than one in 500 (95% confidence limit) and monitoring of much larger numbers should be necessary. The problem of detecting rare effects and of proving causation, however, remains.

To add to the confusion, Professor Lawson emphasises that our study did not give much useful information about reasonably common delayed adverse drug effects or effects arising after long-term use of the compound. This does not seem to us to be relevant to a product used intermittently by injection for short periods in the management of moderate-to-severe pain.

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¹ Lawson, D H, and Henry, D A, *British Medical Journal*, 1977, **1**, 691.

² Lawson, D H, *British Journal of Clinical Pharmacology*, 1979, **7**, 13.

Vitamin B₁₂: an area of darkness

SIR,—In their interesting review on vitamin B₁₂ (1 September, p 533) Professor D M Matthews and Dr J C Linnell state that the early view that cyanocobalamin was the predominant form of vitamin B₁₂ present in the body was not doubted until the early 1960s, when the existence of adenosylcobalamin and methylcobalamin was first demonstrated. May I suggest that their "area of darkness" was perhaps not quite so dark for quite so long?

Already in the early 1950s, only a few years after the isolation of pure cyanocobalamin, biochemists and nutritionists were becoming increasingly aware of the predominant role played by hydroxocobalamin; and in 1955 the late Dr F Wokes and I proposed a hypothetical sulphur-transfer cycle involving hydroxocobalamin in the synthesis of sulphur-containing amino-acids.¹ That hypothesis was based on the clearly stated assumption that hydroxocobalamin rather than cyanocobalamin was the active form of the vitamin present in the body.

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¹ Wokes, F, and Picard, C W, *American Journal of Clinical Nutrition*, 1955, **3**, 383.

Cancer of the ovary

SIR,—I was truly fascinated by the leading article on ovarian cancer (22 September, p 687). As I read the introductory paragraphs on the world-wide differences in racial incidence and the equally interesting demographic and epidemiological data I thought I must write a short note of congratulation—why don't I do this more often, I thought. Reading on, I found a detailed discussion of the ever-expanding field of chemotherapy, the hopes for VP16, and the almost inevitable suggestion that "Greater accuracy in the choice of chemotherapy for individual patients may, in the future, be obtained by drug selection challenges on the xenografted tumours in immune deficient mice or cell colonies obtained from laparotomy specimens." I winced a little as I recalled the extravagant enthusiasm for this approach by oncologists in, for example, Germany at least 20 years ago.