the first time in weeks, and even go out for meals with his friends, for the simple reason that his pain was effectively controlled. He went home (a prospect which had seemed impossible) and spent 10 good weeks there before his final admission.

Dr Lloyd also includes dextromoramide and pethidine in his chart. These are both very short-acting and strongly habituating drugs, which many of us feel have little or no place in the management of terminal pain.

Please don't let us withhold effective pain relief from this group of patients, for whom after all there is often little else that we can offer medically. And let us dispel all myths about these drugs and ensure they are used not only effectively but in good time by the coming generation of doctors on the wards and in the community.

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- ¹ Saunders C. *Nursing Times* July 22 1976: 1133.
² Twycross RG. *Int J Clin Pharmacol* 1974;93:184.
³ Wills LAM. *Postgrad Med J* 1978;54:391-4.

A better system for polio vaccination in developing countries?

SIR,—I read the paper by Dr T Jacob John and others (23 August, p 542) with interest, especially the findings that the oral vaccines tested seemed to have very low potency.

The authors state, "Two batches of imported oral polio vaccine were purchased from the supplier and brought to the laboratory in insulated containers containing ice. They were stored at -20°C and tested for potency just before use. . . ." It is well known that freezing polio vaccine largely inactivates it. This alone could have explained the low potency discovered. I am familiar with the oral vaccine manufactured by Wellcome, which clearly states that freezing is harmful to the vaccine. I assume that other manufacturers also issue the same warnings. This would make the cluster vaccination technique even more impressive than it would have been had Dr John and his colleagues used vaccine which had not been frozen.

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Conversion of thyroxine to triiodothyronine

SIR,—We have read with interest the report of Dr Paul Heyma and colleagues (5 July, p 24), who suggested that the effect of propranolol on thyroxine (T4) conversion to triiodothyronine (T3) was related not to its β -adrenergic blocking activity but to its membrane-stabilising effect. Dr Jones and others in a subsequent letter (p 453) reported that they were unable to show any alteration in T4 conversion to T3 with another (albeit less pronounced) membrane-stabilising β -blocker, oxprenolol. Our recent work with a β_2 -agonist, salbutamol, may help to clarify the problem.

Six healthy females aged 26.7 ± 2.4 years (mean $\pm$ SEM) and weighing 60.3 ± 2.1 kg (an average 8.5% above ideal weight) were given orally 4 mg of salbutamol six hourly for seven days. Serum T4 (Amersham RIA PEG Kit 1M921), T3 (Amersham RIA PEG Kit 1M961), and reverse T3 (Serono Kit 1834) were measured before and at

three, five, and seven days during salbutamol medication. Weight did not alter and serum T4 showed no change. Serum T3 and the T3:T4 ratio showed a slight upward trend but this was not statistically significant. However, both serum reverse T3 and the ratio of reverse T3 to T4 significantly decreased. This suggests that a β_2 -agonist has little action on conversion of T4 to T3 but can alter reverse T3 metabolism.

The fall in the ratio of reverse T3 to T4 together with stable values of T4 and T3 imply that the fall in reverse T3 was the result of enhanced catabolism induced by the β_2 -agonist rather than a decrease in conversion of reverse T3 from T4. This is in agreement with our previous work with laevodopa in semi-starvation states, where laevodopa prevented the usual rise in reverse T3 but had no effect on the fall in T3 despite the maintenance of the resting metabolic rate.¹ Thus it appears that conversion of T4 to T3 may not be under the direct control of β -receptor agonists but that these agonists may directly influence reverse T3 catabolism.

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- ¹ Shetty PS, Jung RT, James WPT. *Proc Nutrition Soc* 1978;38, 18 (abstract).

Nephrotic syndrome with slight proliferative changes: response to prednisone

SIR,—We read with great interest, the recent article by Dr H Rashid and others (2 August, p 347) on the response of patients with the nephrotic syndrome and slight proliferative changes in the glomeruli on light microscopy to prednisolone.

We have studied 16 adult patients who had the nephrotic syndrome and diffuse mesangial proliferative changes on light microscopy. Eleven were treated with prednisolone and five responded. The six who did not respond and five other patients were treated with a combination of cyclophosphamide, dipyrindamole, and warfarin. Of these, eight responded, including two patients who were non-responsive to prednisolone. Thus our overall response rate to both regimens was 81% (13/16). The mean duration of follow-up after remission was 12 months (range 2-43 months).

Treatment of the nephrotic syndrome with diffuse mesangial proliferative changes has shown variable results with different regimens in various studies. Cyclophosphamide and anticoagulants as single agents have been shown to be of use in several studies.¹⁻³ Our results so far indicate that a combination of these agents (cyclophosphamide, dipyrindamole, and warfarin) can be useful not only in patients not responsive to prednisolone but also as therapy of first choice.

Waldherr⁴ has suggested that diffuse mesangial proliferative glomerulonephritis with the nephrotic syndrome evolves from a minimal lesion with the same clinical syndrome. We were able to document this in one of our patients on clinical presentation and during a relapse of his nephrotic syndrome. He respon-

ded to prednisolone on both occasions. In our group of patients, seven (out of 11 who had immunofluorescent studies) had negative staining to all immunoglobulins. Six responded to treatment.

The implications of a diffuse mesangial proliferative glomerulonephritis on light microscopy in patients with the nephrotic syndrome is still unclear. Negative immunofluorescence may predict response to treatment, not only to steroids but also to cyclophosphamide, dipyrindamole, and warfarin. Further work and controlled trials are definitely needed in this area.

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- ¹ German Glomerulonephritis Research Group. *Glomerulonephritis: international conference on pathogenesis, pathology and treatment*. 1977:196-201.

- ² Balslev JL, Brun C, Halberg F, et al. *Acta Med Scand* 1976;200:31-6.

- ³ Cade JR, de Quesada DL, Shires DM, et al. *Nephron* 1971;8:67-80.

- ⁴ Waldherr R, Gubler MC, Levy M, et al. *Clin Nephrol* 1978;10:171-9.

Factor VIII supply and demand

SIR,—Dr J D Cash's comments (23 August, p 565) on my letter (21 June, p 1532) require a brief response.

He states that I failed to mention the availability of plasma for fractionation as an important aspect of the problem of national self-sufficiency in blood products. There was a very good reason for this omission. The Wessex Regional Transfusion Service has recently offered to increase the supply of plasma to the Lister blood products laboratory, only to be told that there was not the capacity to handle the extra plasma.

I think it most important that the repetitive cry for increased plasma does not obscure the very real need for adequate fractionation potential in England today.

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Progesterone, fluid, and electrolytes in premenstrual syndrome

SIR,—Dr Katharina D Dalton (9 July, p 61) draws a distinction between women whose symptoms increase during the premenstrual week but which are none the less present throughout the cycle and women whose symptoms recur regularly during the same phase of each cycle and at no other phase. The latter she considers to be *true* premenstrual syndrome sufferers whereas the former are not. However, this distinction is even more difficult to make than might at first sight appear. For example, in the paper to which Dr Dalton refers¹ the diagnosis of the premenstrual syndrome was sufficiently elastic to include those women whose symptoms begin at or around ovulation, continue throughout the luteal phase, worsen premenstrually, and persist during the menstruum before fading away shortly after the period ceases. How is one to distinguish this "true" premenstrual tension sufferer from the woman whose diary reveals symptoms occurring intermittently during the cycle (but with seven or more days symptom free) with a premenstrual exacerbation?

tion, some menstrual relief, and recurrence of the symptoms shortly after the period ceases? Were Dr Dalton to be really strict and confine the diagnosis of premenstrual syndrome to those women who experience symptoms only during the premenstrual week then the situation might be clearer. But were she to do this she would have to revise drastically downwards her estimate that 50% of actively menstruating women are premenstrual sufferers.²

The symptoms which go to make up the syndrome (tension, anxiety, headache, backache, irritability, depression) are not uncommon; indeed, a recent epidemiological study suggests that they are relatively ubiquitous in women in the age groups studied by Dr Dalton.^{3,4} An additional problem is that to find a woman who is absolutely free of such symptoms at times other than premenstruum can be quite difficult. In the circumstances Dr Dalton's distinction, while of possible theoretical importance, tends to break down in the clinical setting.

Dr Dalton once again reiterates her claim concerning the efficacy of progesterone in the treatment of premenstrual symptoms, despite the fact that two double-blind controlled trials^{5,6} have failed to establish its superiority over placebo. She claims a success rate of 83%; but it should be remembered that other workers have claimed similar rates of success in this condition using substances as diverse as meprobamate, bromocriptine, lithium, and pyridoxine.⁷ Double-blind studies of the efficacy of these substances, however, have also failed to establish their supremacy over placebo. Given that the placebo response rate in the premenstrual syndrome is itself reasonably high, this is a reason not for pessimism, merely for humility.

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³ Banks MH, Beresford SAA. *J Psychosomatic Res* 1979;23:307-13.

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⁶ Sampson G. *Br J Psychiatry* 1979;135:208-15.

⁷ Clare AW. *Br J Psychiatry* 1979;135:576-9.

Health education to improve rubella immunisation in schools

SIR,—Recently I was a school doctor in a girls' comprehensive school of about 800 girls in the borough of Islington. I was shocked to discover that the uptake of rubella immunisation was only 68%. I decided to give a talk to the 150 11-year-olds on the same day as they were given their forms to take home for parental consent to immunisation for rubella. The talk was short—less than 10 minutes. I was gratified by the result—the increase was from 68% to 86%. I was therefore extremely interested in the article by Dr S A M Jones (6 September, p 649) and would agree from my limited experience that it is the children rather than their parents who should be approached about this.

There are four points that I would like to add to her conclusions. (1) The talk to the girls should be the same day as the forms are taken home for parental consent. This will mean the girls will go home full of enthusiasm and less likely to lose the forms. (2) The girls who have consent and are absent on the immunisation day should be immunised at a

medical session later in the term. (3) Girls who failed the previous year should be invited to attend the talk the next year and be given another form. (4) Teachers should be invited to the talk: firstly, to encourage the girls; and secondly, for their own benefit. In this school in two years 10 teachers were suitably impressed by the talk and came to have their blood tested for antibodies.

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Symptoms in middle life and the menopause

SIR,—I was surprised to read Mr J Wilbush's criticism (23 August, p 563) of the masterly survey of symptoms in middle life by Dr G T Bungay and others (19 July, p 181). He is disappointed by "their neglect of basic features of their subject matter." What basic features?

The menopause is a physiological event, like the menarche. It is not a disease and has no known pathology. Certain changes occur in laboratory tests such as vaginal cytology and follicle stimulating hormone (FSH) concentrations in serum, which reflect the changing balance between various endocrine glands, but these are only approximately related to symptomatology. They do not in themselves constitute a disease state and few doctors would be prepared to treat, for instance, a raised FSH concentration in the absence of menopausal symptoms. Symptoms are the basic feature of a menopausal syndrome.

"Symptoms vary with the situational factors obtaining at the meeting between patient and doctor." The transactional nature of the medical consultation has been widely recognised. Some women who regard hormone replacement therapy as desirable following its promotion in the lay press, knowing that it is often prescribed for flushes, may complain of flushes to a sympathetic doctor in order to put pressure on him to prescribe hormones. The doctor may be aware of this; but this does not mean that he can ignore the patient's symptoms, which are his chief guide to her clinical needs.

"What do these studies prove?" They show that both men and women in the Oxford area complain of such symptoms as headache, loss of interest in sex, frequency of micturition, low backache, difficulty in sleeping, and crawling and tingling sensations in the skin. They show that these symptoms are not particularly related to the menopause, although some of them have previously been described as "menopausal."¹ They confirm the association of vasomotor symptoms with the menopause,² and the premenopausal peak of minor mental symptoms described by other workers.³

W H Utian carried out a single-blind placebo controlled study of oestrogen therapy in menopausal patients and found that the only symptoms to respond to oestrogen better than placebo were those related to hot flushes and atrophic vaginitis.⁴ In a double-blind placebo controlled trial of conjugated equine oestrogens we found that only hot flushes and vaginal cytology showed a significant improvement on oestrogen compared with placebo. All the other symptoms tested (headache, insomnia, arthralgia, depression, etc), did not show a greater improvement on oestrogen than on placebo.⁵ In a further double-blind placebo controlled trial of piperazine oestrone sulphate in the treat-

ment of menopausal depression and flushing, we found that flushes responded significantly on oestrogen compared with placebo, but depression showed no greater improvement on oestrogen than on placebo, when measured by the Beck Depression Inventory.⁶

The prescription of hormone therapy for "menopausal" symptoms should be limited to those symptoms which have been shown to be menopausal and oestrogen-responsive by epidemiological surveys and controlled trials.

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Progestogens before and after the menopause

SIR,—In your leading article on oestrogen-replacement therapy in old age (30 August, p 572) you refer to the evidence from Meade and his colleagues¹ that the progestogen component in combined oral contraceptives may be associated with the increased risk of arterial disease in pill users. It was unfortunate that similar evidence from the Royal College of General Practitioners' Oral Contraception Study² was in press at about the same time, so that neither paper was able to draw attention to the value of the confirmation of the observation from two independent data sets.

You rightly suggest the possibility that the addition of progestogen to an oestrogen regimen in climacteric women might also increase the risk of arterial disease. I have also expressed that view.³ I believe, however, it is important not to assume too readily that observations in premenopausal women can be applied to postmenopausal women, particularly when the treatment is somewhat different. A recent report by Weiss and Sayvetz⁴ identifies one mechanism that may be the same during the reproductive and postreproductive periods. They showed that oral contraceptive users have a reduced incidence of endometrial carcinoma when compared to non-users, and they attribute this benefit to the progestogen component, an effect which is well established in postmenopausal hormone therapy.

In our own data, eight cases of endometrial cancer have been reported. Six of these have occurred in the control subjects who have never used oral contraceptives, two in former users, and none in current users. The associated periods of observation are 129 593 person-years in the control group, 78 142 in the ex-user group, and 98 551 person-years in the current-user group.

Only one case (Vessey, personal communication) has been reported in the Oxford/FPA Study.⁵ This patient entered the study while using a diaphragm and had not used the pill at any time when endometrial cancer was diagnosed six years later. The associated periods of observation among women entering the study while using the pill, the diaphragm, and the intrauterine device are currently 73 382, 33 521, and 24 049 women-years respectively.

In both studies the subjects have predominantly used the combined oral contra-