continuing and expanding research on the treatment of this condition, which is at present responsible for considerable personal distress and social disruption. In view of the large numbers of women between the menarche and the menopause who suffer from PMS any significant reduction in its overall incidence will be welcome and we hope that family doctors will be encouraged to treat PMS by these new approaches. Further help and support from specialised clinics in teaching hospitals and other centres will be required for some time yet, but we hope soon to publish further observations on the clinical presentation of PMS which will minimise this need.

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- ¹ Weissman, M M, and Klerman, G L, *Archives of General Psychiatry*, 1977, **34**, 98.
- ² Pollitt, J, *Proceedings of the Royal Society of Medicine*, 1977, **70**, 145.
- ³ Munday, M R, et al, *Journal of Endocrinology*, 1977, **73**, 21P.
- ⁴ Munday, M R, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 16.
- ⁵ Brush, M G, et al, Abstract, International Symposium on Prolactin, Nice, France, 1977.
- ⁶ Munday, M R, and Brush, M G. Unpublished observations.
- ⁷ Backstrom, T, and Carstensen, H, *Journal of Steroid Biochemistry*, 1974, **5**, 257.
- ⁸ Backstrom, T, et al, *Journal of Steroid Biochemistry*, 1976, **7**, 473.
- ⁹ Benedek-Jaszmann, L J, and Hearn-Sturtevant, M D, *Lancet*, 1976, **1**, 1095.
- ¹⁰ Halbreich, U, et al, *Lancet*, 1976, **2**, 654.
- ¹¹ Brush, M G, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 9.
- ¹² Taylor, R W, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 35.
- ¹³ Kerr, G D, *Current Medical Opinion and Research*, 1977, **4**, suppl 4, p 29.

Anaphylaxis after dichloralphenazone treatment

SIR,—The case of anaphylactic response to the ingestion of dichloralphenazone (Welldorm) tablets (reported by Dr Steven Perl, 5 November, p 1187) is by no means unique.

Two Welldorm tablets were administered as night sedation to a 55-year-old man awaiting a minor surgical operation. Within minutes he developed severe bronchospasm and a widespread bullous skin eruption. The bronchospasm responded readily to injection of hydrocortisone and aminophylline. By the following morning there was no evidence of any lesion.

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Silk sutures in the common bile duct

SIR,—Having twice had a similar experience to that described by Mr B I Rees and Mr G Jacob (12 November, p 1265)—although on both occasions the recurrent common bile duct stone contained a thread rather than a silk suture—I was interested last year to remove three stones from the common duct of a woman who had had a cholecystectomy eight years before. Each stone contained a thread suture, and reference to the excellent original operation note produced the explanation: the cystic duct and two cystic arteries had been tied with thread.

I agree that it is important that no unabsorbable suture should be used in the vicinity of the common duct. It is not uncommon to

find that surgeons in training recognise this risk so far as the cystic duct ligature is concerned, but many are unaware that the cystic artery tie also may discharge itself into the common duct. The chances of this happening are presumably greater if an exploration of the common duct has been performed, but a small abscess around the foreign body on the artery can undoubtedly discharge into the lumen of the nearby common duct even when its wall is surgically intact.

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Anaphylactoid reactions to dextran 70

SIR,—I read with interest the report by Dr L H Fanous and others of two cases of anaphylactoid reaction to dextran 70 (5 November, p 1189).

The cases which we reported last year¹ had no history of asthma and did not develop urticarial rashes. Investigation of the immunological aspects of these cases did not reveal the cause. It is peculiar that in our hospital there have been no cases of this type reported in the general surgical or medical wards and that the syndrome appears to be associated with maternity cases.

The question of particles in the dextran solutions and bacteriological contamination of these solutions were investigated with negative results at the time. As an anaesthetist I have meanwhile continued to give dextran as a prophylaxis against deep venous thrombosis in orthopaedic cases, but more recently there has been apprehension about dextran as a precipitating factor in postoperative acute renal failure, as a result of a paper by Feest,² and the practice here now is to not give dextran to those orthopaedic patients who have a blood urea concentration higher than normal for their age.

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- ¹ Fothergill, R, and Heaney, G A, *British Medical Journal*, 1976, **2**, 1502.
- ² Feest, T G, *British Medical Journal*, 1976, **2**, 1300.

Lichen-planus-like eruption: a marker for chronic graft-versus-host reaction

SIR,—In regard to your leading article (23 July, p 211) on skin changes after bone marrow transplantation we would like to make the following comments. Since our initial report¹ of four patients with lichen-planus-like eruption (LPLE) after bone marrow transplantation we have seen seven additional cases.² We have found that the clinical spectrum of LPLE may be compared to the various clinical aspects of idiopathic lichen planus (ILP). The occurrence of LPLE after bone marrow graft not only would throw light on the pathogenesis of ILP^{2,3} but also has a practical interest in the management of patients after grafting.

Indeed, we have found that: (1) a graft-versus-host reaction always precedes development of the LPLE; (2) LPLE never occurs if the graft is rejected; and (3) LPLE always occurs in a context of "persistent graft-versus-host reaction." These data strongly support the concept of LPLE actually representing a skin manifestation of graft-versus-host disease.³ In every case the first

symptoms of LPLE were found in the mouth. This oral involvement was very similar to ILP; it can be easily recognised by a dermatologist and is quite different from drug-induced erosive leukokeratosis and from candidiasis. The oral LPLE represents, therefore, a useful early marker of chronic graft-versus-host disease and a tool for clinical evaluation and therapeutic guidance in patients undergoing bone marrow transplantation.

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- ¹ Saurat, J H, et al, *British Journal of Dermatology*, 1975, **92**, 591.
- ² Saurat, J H, et al, *British Journal of Dermatology*, 1975, **93**, 675.
- ³ Saurat, J H, and Gluckman, E, *Clinical and Experimental Dermatology*. In press.

Adverse reactions to intravenous thiopentone

SIR,—We were interested to read the article by Drs J M Evans and J A M Keogh (17 September, p 735) in which they reported three histaminoid-type reactions to the intravenous use of thiopentone. In view of the relative rarity of adverse reactions to this agent¹ we would like to report a further case.

A 33-year-old White man underwent a routine repair of a right inguinal hernia. Routine premedication with atropine plus Omnopon was given and intravenous thiopentone and suxamethonium used for induction of anaesthesia. The operation was uneventful. Postoperatively the patient developed severe bronchospasm, generalised erythema, pruritus, and gross facial oedema. His white cell count remained normal but showed a 6% eosinophilia. Treatment was instituted with high-dose steroids and the antihistamine chlorpheniramine. The bronchospasm settled rapidly, but the erythema and oedema gradually resolved over the following 72 h.

This patient had a known hypersensitivity to penicillin and tetanus toxoid and eight years previously had undergone an operation for treatment of a compound fracture of his right lower leg. In view of the common use of thiopentone for induction, it is likely that previous use had sensitised the patient to this agent, resulting in a type I hypersensitivity reaction on re-exposure.

As noted by Drs Evans and Keogh, histaminoid-type reactions are probably encountered more frequently than reported and it would seem justified to advocate the prophylactic use of an antihistamine in patients known to be hypersensitive to exogenous agents.

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- ¹ *British Journal of Anaesthesia*, 1976, **48**, 57.

Bell's palsy and herpes simplex

SIR,—Dr B E Juel-Jensen (22 October, p 1086) has taken exception to the evidence that I presented (24 September, p 829) which appeared to support the hypothesis that Bell's palsy may be associated with herpes simplex virus (HSV) infection. While his own studies, to which we are given no reference, resulted in a conclusion contrary to three of the references I cited, he is correct to confirm that there is no definite proof of the association. However, in his determination to demonstrate that the patient in my report did not have

herpes simplex stomatitis he does himself an injustice.

The patient had the typical triad of an acute febrile illness, mouth ulcers, and cervical lymphadenopathy with no rash or genital ulcers and no past history of cold sores. Diagnosis was possible without laboratory investigations. The antibody titre to HSV was >1280 , and for varicella zoster (VZ) the titre was >1280 ; and it is therefore difficult to see why lack of this numerical information should cause comment when the titres had been stated as being "very high." It is recognised that in primary herpes in young adults there may be a rise in the VZ antibody titre, but the converse is not true. There is no massive rise in the HSV titre in zoster. It seems reasonable to accept these titres as confirmation of the clinical diagnosis. To suggest that the patient had concurrently both primary herpes stomatitis, which is rare in adults, and facial paralysis due to zoster (what used to be called the "Ramsay Hunt syndrome"), also uncommon, hardly strengthens Dr Juel-Jensen's case. It is unlikely that paired sera in this instance would have clarified the position. That culture was not undertaken is unfortunate not because the diagnosis needed further confirmation but because it is not known whether it was a type I or type II infection. There is some evidence, I understand, that type II infections tend to cause a rise in both HSV and VZ titres and it was a type II infection that was implicated in the only other report of Bell's palsy in association with HSV infection. Finally, Dr Juel-Jensen suggests that perhaps the mouth ulcers were unilateral and therefore due to zoster. It would seem that his reading of my report was incomplete, for it was stressed that the ulcers were generalised, a fact to which considerable importance had been attached.

Perhaps no connection does exist between HSV and Bell's palsy, but it would be wiser for the present to remain undecided rather than discount the possibility because this evidence is not consistent with a personal opinion, however authoritative its source.

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Saliva carbamazepine levels in children

SIR,—The usefulness of saliva levels for monitoring phenytoin therapy is well established^{1,2} and recent studies indicate that it may be possible to use salivary concentrations of carbamazepine³⁻⁵ and, with more difficulty, phenobarbitone⁴ in a similar way. These studies, however, were mainly carried out on adult patients. Little is known of anticonvulsant drug pharmacokinetics in children, and the relationship between plasma level and clinical effect is usually assumed to be similar to that in adults.

We have measured plasma and saliva concentrations of carbamazepine in 15 patients aged 3-14½ years receiving long-term treatment with carbamazepine to determine whether a correlation exists in children. Mixed saliva was collected (using a mucus extractor for younger children) after stimulating flow with a few crystals of citric acid and strawberry flavouring powder placed on the tongue. Saliva samples were collected at the time of blood sampling, which was being carried out as part of routine patient management. Samples were frozen at -20°C until assayed for carbamazepine by a modification of the GLC method of Least *et al.*⁶

There was a good correlation between the saliva and plasma levels of carbamazepine ($r=0.87$, $P<0.001$), and the saliva:plasma ratio resulting, 0.30 ± 0.07 (mean $\pm$ SD, $n=17$), is similar to the saliva:plasma³ and CSF:plasma⁷ ratios in adults and to the reported free fraction of drug in adult plasma.⁴

We have used saliva levels in a preliminary study of dose frequency requirements for carbamazepine in children. Using the methods described above, serial saliva samples were obtained from children in hospital and assayed for carbamazepine. The figure shows results obtained in a boy receiving carbamazepine 400 mg twice daily for temporal lobe epilepsy.

Saliva carbamazepine concentrations after administration (arrows) of 400 mg twice daily. Circle indicates plasma carbamazepine concentration $\times 30$. Broken line indicates predicted minimum therapeutic level. Conversion: SI to traditional units—carbamazepine: $1 \mu\text{mol/l} \approx 23.6 \mu\text{g/100 ml}$.

The saliva concentration rose steadily after drug administration (2×200 mg proprietary tablets), reaching a maximum of $10.8 \mu\text{mol/l}$ ($255 \mu\text{g/100 ml}$) after 4.5 h and then declining to minimum levels of $5.6 \mu\text{mol/l}$ ($120-140 \mu\text{g/100 ml}$).

Although the therapeutic range of plasma carbamazepine levels in the treatment of epilepsy has not yet been established, we have accepted a level of $18-50 \mu\text{mol/l}$ ($425-1180 \mu\text{g/100 ml}$) to be optimum on the basis of studies relating plasma levels and clinical effects in adults.^{5,8} The equivalent range in saliva is $5.5-15 \mu\text{mol/l}$ ($130-355 \mu\text{g/100 ml}$). The saliva levels of the patient illustrated here were within this "predicted" therapeutic range and the patient was judged to be clinically well controlled before this study was carried out.

Although the patient was in a "steady state," large daily fluctuations in drug concentration were observed and illustrate how misleading a single level may be if taken at random between doses. The magnitude of the daily fluctuation is probably greater in children than in adults receiving the same dose regimen since the rate of carbamazepine elimination appears to be more rapid in the former age group. As part of a larger study the saliva half life of carbamazepine was determined in the patient described above while receiving single daily doses of the drug. The value obtained was 7.3 h and this agrees with previous findings⁹ that the rate of elimination of carbamazepine in children is greater than in adults.

In the case illustrated saliva samples taken within 1 h of drug administration gave no indication of contamination by unabsorbed drug, but when crushed tablets in orange juice were given to a 3½-year-old child con-

tamination was detected up to 1.5 h after administration.

Saliva levels appear to provide a means of monitoring carbamazepine therapy, enabling the dose to be tailored to suit individual requirements. Care must be taken, however, that there is no contamination by unabsorbed drug. This method also provides a valuable means of studying drug pharmacokinetics. Further work on carbamazepine and phenytoin dosage requirements in children (including the distribution and elimination of the active metabolite of carbamazepine, carbamazepine-10,11-epoxide) is being undertaken.

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- ¹ Reynolds, F, *et al*, *Lancet*, 1976, **2**, 384.
- ² Paxton, J, *et al*, *Lancet*, 1976, **2**, 639.
- ³ Chambers, R E, *et al*, *Lancet*, 1977, **1**, 656.
- ⁴ McAuliffe, J J, *et al*, *Neurology*, 1977, **27**, 409.
- ⁵ Troupin, A, *et al*, *Neurology*, 1977, **27**, 511.
- ⁶ Least, C J, Johnson, G F, and Solomon, H M, *Clinical Chemistry*, 1975, **21**, 1658.
- ⁷ Troupin, A S, and Friel, P, *Epilepsia*, 1975, **16**, 223.
- ⁸ Morselli, P L, and Frigerio, A, *Drug Metabolism Reviews*, 1975, **4**, 97.
- ⁹ Rane, A, Höjer, B, and Wilson, J T, *Clinical Pharmacology and Therapeutics*, 1976, **19**, 276.

Shortage of anaesthetists

SIR,—All correspondents on this subject have concentrated on manning by full-time anaesthetic specialists and have chosen to ignore the large number of doctors in general practice who possess the DA, many of whom no longer administer any anaesthetics.

I have no doubt that the majority of these doctors would be willing and indeed delighted to spend a few sessions a week in the hospital confines giving anaesthetics were it not to their financial detriment to do so. I am not suggesting that these part-time (though basically qualified) anaesthetists should be carrying out thoracic or neurosurgical lists, but there is little else from which they should be barred and they could be supervised in the same manner as junior staff by their consultants.

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The other handicap: brightness

SIR,—It is encouraging to see the problems of the gifted child being brought to the attention of doctors by Mr M E Lobascher and Dr N P C Cavanagh (12 November, p 1269). Their article rightly points out the role that education authorities should, but in some cases do not, play in helping these children.

However, there is an organisation, the National Association for Gifted Children, which was formed 10 years ago specifically to aid these children and advise their parents, who are often completely bewildered by the needs of such a child. The association has branches all over the country. Besides giving advice, it holds meetings where parents can discuss their mutual problems and meetings where children can take part in a variety of intellectual and physical activities and have the chance to make friends with others of like interests and ability.

The association is always willing to give advice to and co-operate with any doctor who finds he may have one of these "other"