SLE precipitated by antibiotics in Sjögren's syndrome

SIR,—In his letter (17 January, p 152) about the recent article on this subject by my colleagues and myself (15 November, p 385) Dr J R Sewell makes four main points: (1) Our case of systemic lupus erythematosus (SLE) did not meet current diagnostic criteria for SLE; (2) neither LE cells, abnormalities in DNA binding, nor pericarditis are specific to SLE; (3) the abnormalities in DNA binding we reported might have been due to treatment with an anti-inflammatory drug; and (4) the patient's second disease exacerbation was a consequence of pneumonia. We wish to make the following comments in reply.

(1) Our patient has shown the following disease features at some time in the course of her illness: polyarthritis without deformity, Raynaud's phenomenon, rash, pericarditis, more than two classical LE cells in a blood film, and DNA binding of 60%. The first five of these are included in the preliminary criteria for the classification of SLE proposed by the American Rheumatism Association (1971), four of which were considered necessary for diagnosis. In a "short report" we were of necessity succinct, and the Raynaud's phenomenon and rash were not specifically mentioned in the article.

(2) We would certainly agree with Dr Sewell that neither pericarditis, nor the finding of LE cells in a blood film, nor an abnormal DNA binding are specific to SLE—we did not suggest that they were.

(3) Before the patient's later disease exacerbation she had been taking ibuprofen and this was continued subsequently when she was well apart from her joint symptoms and DNA binding was normal. Thus the 60% DNA binding in her blood could not be explained by anti-inflammatory drug administration, although co-trimoxazole, as we stated in the article, may well have precipitated the two exacerbations of her disease.

(4) The confusion, pyrexia, and weakness in the second episode described in our patient responded only to the administration of high-dose steroids, and this clinical improvement occurred in parallel with change in DNA binding and fall in antinuclear factor titre. Had the clinical features been the result of pneumonia this would have been the case.

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High plasma calcitonin levels in breast cancer

SIR,—Dr R C Coombes and his colleagues (25 October, p 197) report increased levels of immunoreactive calcitonin in the plasma of 23 out of 28 patients with metastatic carcinoma of the breast. We have recently completed a similar study¹ and are pleased to be able to confirm their findings.

In our laboratory 44 women aged 30-91 years with histologically proved breast cancer were studied; 29 had widespread metastatic involvement and the others had localised disease. Three-quarters of the patients with metastatic disease who were not receiving current therapy had high plasma calcitonin values (up to 1070 ng/l; normals <260 ng/l). Interestingly, patients recently treated with irradiation or chemotherapy had normal values.

Only one patient with apparently localised disease had a high value. It appears that the measurement of calcitonin may have important diagnostic, therapeutic, and prognostic indications as a marker in breast cancer.

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¹ Silva, O L, Chisholm, R C, and Becker, K L, *Clinical Research*, 1975, 28, 596A.

Tryptophan and depression

SIR,—The report of a double-blind multicentre study from four Scandinavian hospitals,¹ with its subsequent elaboration by Dencker at the symposium held recently at the Royal College of Physicians (leading article, 31 January, p 242) is a remarkable development in the evolution of the psychopharmacological role of the amino-acid tryptophan. Encouraged by this, we are making a preliminary report on a comparative evaluation of L-tryptophan and imipramine using a randomised double-blind design.

So far 16 inpatients with depressive illness, broadly selected on the criteria adopted by the Clinical Psychiatry Committee of the Medical Research Council,² have completed the trial successfully. The second and the third of these criteria were modified to the extent that the previous duration of the illness should not be less than four weeks and that the patient should not have received any specific treatment for the present episode of illness. The Hamilton rating scale for depression was used to quantify the depression on admission to the trial and at the end of four weeks. All patients received a fixed regimen of medication—either six 25-mg tablets of imipramine daily and 12 tablets of L-tryptophan placebo or six tablets of imipramine placebo and 12 tablets of L-tryptophan, each containing 0.5 g of the amino-acid together with 5 mg of pyridoxine hydrochloride and 10 mg of ascorbic acid. Thus each patient received a total of six tablets three times a day. To ensure further the double-blind nature of the trial the patients were instructed to discuss the possible side effects with a staff member other than the rater, as we observed initially that the subjects taking genuine imipramine could reveal themselves because of their common anticholinergic side effects.

As can be seen in the accompanying table our results are consistent with those of Jensen and his colleagues.¹ It was shown that there was no statistically significant difference between the two groups and that L-tryptophan and imipramine were equally effective in the treatment of these cases of depression. Our trial differs from that carried out by Jensen and his colleagues in that they used L-tryptophan without added vitamins. Winston³ has postulated that the good results of a recent trial⁴ of L-tryptophan in depression

may have been due to the fact that in that study pyridoxine was omitted from the commercially available tablet. Our own results suggest that pyridoxine does not detract from the antidepressant properties of L-tryptophan.

We thank Mr Jack Desty of Cambrain Chemicals Ltd for supplying the L-tryptophan tablet (Optimax) and other trial materials and we are grateful to the other staff members of our department for their co-operation.

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¹ Jensen, K, *et al*, *Lancet*, 1975, 2, 920.

² Clinical Psychiatry Committee of the Medical Research Council, *British Medical Journal*, 1965, 1, 881.

³ Winston, F, *Lancet*, 1975, 2, 868.

⁴ MacSweeney, D A, *Lancet*, 1975, 2, 510.

Warfarin and Distalgesic interaction

SIR,—A 28-year-old woman who had developed a venous thrombosis after a Pott's fracture was referred to this laboratory for supervision of anticoagulant therapy. On 31 December 1975 her prothrombin ratio (BCR) was 3.2 and the dose of warfarin was lowered to 6 mg daily. On 7 January her BCR was 1.54 so the dose was increased to 7 mg. On 19 January BCR was 3.35 and warfarin was omitted for a day. She denied either any change in dietary habits or taking any drugs except for two Distalgesic tablets in the evening of 18 January. On 20 January she presented with haematuria and loin pain and had taken "a few more" Distalgesic tablets on 19 January. BCR was 5.2 and 2 mg of vitamin K₁ was given intravenously. The haematuria and pain ceased on 21 January.

I had been unable to explain why she had gone out of control, but in the light of the communication from Dr M Orme and others (24 January, p 200) I now assume that it was because of warfarin and Distalgesic interaction.

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Myasthenic syndrome during treatment with practolol

SIR,—We wish to report an apparent complication of practolol therapy.

The patient, born in 1921, was a wheezy bronchitic hypertensive whose blood pressure in 1969 was persistently elevated (220/195/120-105 mm Hg). Practolol was given in increasing doses, with bendrofluazide 5 mg and Slow-K 600 mg daily. His blood pressure on practolol 2400 mg daily had fallen to 140/70 mm Hg and he remained well until October 1972, when he presented with an eight-month history of double vision on watching football matches or long films, culminating in a two-day episode of bilateral ptosis. All the above symptoms were relieved by rest. There was no evidence symptomatically or on examination of

Hamilton rating scale scores before and after treatment with L-tryptophan and imipramine

Time of rating	L-Tryptophan (n = 9)			Imipramine (n = 7)			t value of intergroup differences
	Mean	t value	Significance	Mean	t value	Significance	
On admission	25.33			22.86			0.77 (NS)
After four weeks	4.67	8.58	P<0.01	3.00	18.73	P<0.001	0.28 (NS)

weakness in any other muscle groups. Two separate Tensilon tests (10 mg edrophonium chloride) with saline control were performed in a double-blind manner. After the first injection of edrophonium chloride the ptosis improved greatly, and two days later with the second test the improvement was less marked. After the Tensilon tests all therapy was stopped and the patient referred to the late Professor Andrew Wilson, who suggested that this myasthenic syndrome might be related to the practolol. Electromyography revealed no abnormality, nor did it six months later, when the patient had been off all therapy. Investigations including ESR, haemoglobin, blood urea and electrolytes, thyroid function tests, and x-rays of the mediastinum revealed no abnormality. The myasthenic symptoms have not recurred following the second dose of edrophonium chloride, but because the patient's blood pressure rose after stopping the practolol he was restarted on spirinolactone 100 mg daily and bendrofluazide 5 mg daily.

As remission may occur in myasthenia gravis perhaps a three-year follow-up period is too short to be sure that relapse will not occur. However, as the principal adverse effects associated with the use of practolol affect the eyes, skin, aural and nasal mucous membranes, and mesentery (14 June, p 577) and we have seen no mention of a muscular syndrome, we feel it worth alerting clinicians to the possibility of this syndrome being associated with practolol.

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An unnecessary risk to children

SIR,—While I have considerable sympathy with the general contention that children should remain in the back seat (leading article, 24 January, p 180), in the present state of the law on seat belt equipment this may serve actually to increase the incidence of death and injury rather than reduce it. This arises because less than 1% of cars have seat belts in the rear seat, since they are not a mandatory requirement, and children between the ages of 8 and 14 rarely use the child type of harness. In these circumstances it is quite conceivable that it is safer to be in the front seat belted up than in the back seat unbelted.

While the article quoted some statistics, these were not on a comparative basis. In particular, the extent to which the front seat risk is higher than that for the rear and the savings likely to be brought about by the wearing of seat belts in each location. It may be that an expansion of your analysis would indicate that mandatory fitting of belts to the rear seats is a more beneficial proposal.

It continues to be important that new legislation is reasonably likely to bring about an improvement just as the effectiveness of new medications should be proved. Otherwise the public is brought into increasing conflict with the police for no benefit.

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Dukes classification of carcinoma of the rectum

SIR,—In your leading article (13 December, p 605) entitled "Search for presymptomatic large bowel cancer" it is stated that "on the

Dukes classification stage A is a tumour limited to the submucosa, B is with invasion through the muscularis without nodal metastasis, and C with spread to the nodes." With regard to group A and to some extent also to group B this seems to be wrong.

In the original article¹ and later papers and monographs by Dukes^{2,3} the definitions given are: in group A cases the growth is limited to the rectal wall (also including cases infiltrating into but not outside the muscularis propria); in group B the growth has infiltrated into the perirectal tissue but has not reached the regional lymph nodes; and in group C there are metastases in the lymph nodes. These groups are well illustrated by Dukes in the original paper and later articles.

As the Dukes classification for cancer of the large bowel is used world-wide it seems most important that workers in this field, in stating that this classification has been used, should adhere to the definition given by Dukes himself to ensure as strict comparability of material and results as possible.

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- ¹ Dukes, C. E., *Journal of Pathology and Bacteriology*, 1932, **35**, 323.
- ² Dukes, C. E., *Journal of Pathology and Bacteriology*, 1940, **50**, 527.
- ³ Dukes, C. E., *Cancer of the Rectum*, p 66. Edinburgh and London, Livingstone, 1960.

* * * Dr Lindström is quite right; we quoted a widely used American version of the Dukes classification which, as he points out, is inaccurate. We agree that the definitions originally proposed by Dukes should be retained for international use.—ED, *BMJ*.

Folic acid deficiency during intensive therapy

SIR,—We have followed the recent papers on this subject^{1,2} and the ensuing correspondence³⁻⁵ with great interest. Ibbotson *et al*¹ point out that we did not state the exact type of intravenous nutrition in our paper⁶ and so we have now received our two cases. The first patient, who had a short illness following mitral valve replacement, received saline and dextrose only, while the second, who had septicaemia and renal failure, received Aminosol (without ethanol) for six days in his terminal illness. However, circulating megaloblasts were seen as early as 24 hours after commencing this treatment. There is no evidence that either patient received ethanol.

Although our two cases fit into the syndrome of rapidly developing folate deficiency during intensive therapy, they showed in addition extremely bizarre features (for example, giantoblasts, dyserythropoietic changes, frequent multinucleate cells, vacuolation) superimposed on the more usual megaloblastic changes. These additional changes may have been due to factors such as infection, drugs, uraemia, anoxia, etc, having a direct effect on erythropoiesis.

On an historical note, Ibbotson *et al*¹ inferred from our paper that the first description of this bizarre megaloblastic and dyserythropoietic anaemia of rapid onset occurring in seriously ill patients was that of Limarzi and Levinson.⁷ In fact we attributed this to an earlier paper by Harvier and Mallarmé published in 1938.⁸ Unfortunately this date was misprinted as 1968 in the list of references.

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- ¹ Wardrop, C A J, *et al*, *Lancet*, 1975, **2**, 640.
- ² Ibbotson, R M, Colvin, B T, and Colvin, M P, *British Medical Journal*, 1975, **4**, 145.
- ³ Wardrop, C A J, *et al*, *British Medical Journal*, 1975, **4**, 344.
- ⁴ Ibbotson, R M, Colvin, B T, and Colvin, M P, *British Medical Journal*, 1975, **4**, 522.
- ⁵ Colvin, B T, and Ibbotson, R M, *Journal of Clinical Pathology*, 1975, **28**, 1007.
- ⁶ Saary, M, *et al*, *Journal of Clinical Pathology*, 1975, **28**, 324.
- ⁷ Limarzi, L R, and Levinson, S A, *Archives of Pathology*, 1943, **36**, 127.
- ⁸ Harvier, P, and Mallarmé, J, *Sang*, 1938, **12**, 883.

Neonatal jaundice in association with operative delivery

SIR,—I read with interest Professor E A Friedman and Mr M R Sachtleben's paper (24 January, p 198) and their suggestion that clinically undetectable focal haemorrhage secondary to instrumental delivery might be a major contributory factor in the rising incidence of neonatal jaundice. I would like, however, to bring to their attention our findings published in August 1974.¹

On analysis of the full-term infants admitted to the special care unit of the Simpson Memorial Maternity Pavilion, Edinburgh, for hyperbilirubinaemia we similarly found no clear relationship with oxytocin administration, but the Kielland forceps delivery rate for the group was twice the mean for the hospital over the same period. Our conclusion was that the cumulative effects of induction plus operative vaginal delivery even near term probably produces a number of neonates not totally prepared for extrauterine life. In particular their hepatic conjugating mechanism might remain untriggered. We felt that focal haemorrhage too small to be clinically detected was unlikely to elevate the serum bilirubin concentration to such levels.

The morbid effects upon the fetus of modern obstetric practice must constantly be balanced against the undoubted rapid fall in mortality. With increasing vigilance of detection and improved treatment we have, as yet, no evidence that the "boom" of jaundiced babies has produced significant long-term effects on our population.

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- ¹ Eden, O B, Revolta, A D, and Adjei, S K, *British Medical Journal*, 1974, **3**, 573.

Computers and privacy

SIR,—Your leading article on this subject (24 January, p 178) is of particular interest to this practice. Since August 1975 we have been using a computer to maintain our medical records in total. We are particularly concerned with confidentiality and your last paragraph sums up our conclusions exactly.

Each doctor has a unique secret password into the system. We also have a "p p" password which we release to our medical secretaries so as to allow them access to the records.