low. It is difficult to know what the second figure "1 in 450 000 to 1 in 1 800 000" is intended to denote. It is presumably meant to imply that the average size of population expected to include nine such patients is 450 000-1 800 000. This figure is probably too high but in any case the total population from which the nine patients were ascertained is undefined and presumably unknown. The probability that the size of this population falls within 95% confidence limits of the above estimate is likely to be quite high. Moreover, three specialised rheumatological centres were involved so that the likelihood of biased ascertainment is considerable.

Among 104 successive men with ankylosing spondylitis ascertained here, one has sero-positive peripheral erosive polyarthritis with a rheumatoid olecranon nodule, his HLA typing including B27. The prevalence of this grade of rheumatoid arthritis is 1% in males.⁴

We therefore interpret the evidence as providing no support for a non-random association of the two diseases and indeed it would be surprising and even more interesting if such cases were not encountered. All the present clinical, immunological, and genetic evidence points to the likelihood that there is no aetiological connection between rheumatoid arthritis and ankylosing spondylitis.

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¹ West, H F, *Annals of the Rheumatic Diseases*, 1949, 8, 143.

² de Blécourt, J J, Polman, A, and de Blécourt-Meindersma, I, *Annals of the Rheumatic Diseases*, 1961, 20, 215.

³ Lawrence, J S, *British Journal of Clinical Practice*, 1963, 17, 699.

⁴ Kellgren, J H, and Lawrence, J S, *Annals of the Rheumatic Diseases*, 1956, 15, 1.

Aplastic anaemia and hair dye

SIR,—The anecdotal report by Drs P J Toghill and R G Wilcox (28 February, p 502) implies a relationship between the occurrence of aplastic anaemia and use of a hair dye. The authors reported prior exposure of the patient to oxytetracycline and penicillin but state that it is unlikely that either antibiotic caused the patient's aplastic anaemia. Aplastic anaemia has been recorded in conjunction with use of tetracycline, chlortetracycline, demethyl chlortetracycline, and doxycycline as well as phenoxymethyl penicillin, cloxacillin, and ampicillin.¹ Attention is drawn to the risk of thrombocytopenia and neutropenia in connection with use of oxytetracycline,² and a fatal case of aplastic anaemia possibly due to oxytetracycline has been described.³

Three publications dealing with long-term exposure of mice,⁴ rats,⁵ and dogs⁶ to hair dyes give no indication of deleterious effects on bone marrow or peripheral blood elements. Data from current industry studies,⁷ which include *para*-toluenediamine at a concentration as high as 6% and both nitrophenylenediamines, show no evidence of toxic effects of these or any other hair dyes on bone marrow. Most of these data were discussed by Burnett at the 1975 meeting of the European Cancer Society in Nottingham.

Karch and Lasagna⁸ emphasise the difficulties in relating specific untoward events to drugs. They categorise adverse drug reactions into definite, probable, conditional, and doubt-

ful subgroups. In the light of the data referred to above one is forced to conclude, using these definitions, that the fatal case of aplastic anaemia described by Drs Toghill and Wilcox was probably if not definitely due to either oxytetracycline or penicillin and that it is doubtful that the hair dye in question was causal. Moreover, since 20% of women in the United Kingdom are current users of hair colouring products (and many more have used these products at some time) one would expect to find a history of hair colour usage clearly associated with several cases of a disease before drawing any conclusion. Thus I would support Drs Toghill and Wilcox's plea for careful questioning and continuing inquiry in the case of any unusual phenomenon.

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¹ Committee on Safety of Medicines, Register of Adverse Reactions Vol. III.

² *Physicians' Desk Reference*, Oradell, New Jersey, Medical Economics Co, 1976.

³ Kishore, B, et al, *Indian Journal of Medical Sciences*, 1969, 32, 137.

⁴ Burnett, C, et al, *Food and Cosmetics Toxicology*, 1975, 13, 353.

⁵ Kinkel, H J, and Holzman, S, *Food and Cosmetics Toxicology*, 1973, 11, 641.

⁶ Wernick, T, Lanman, B, and Fraux, J, *Toxicology and Applied Pharmacology*, 1975, 32, 450.

⁷ Burnett, C, and Lanman, B, in preparation.

⁸ Karch, F E, and Lasagna, L, *Journal of the American Medical Association*, 1975, 234, 1236.

Spasmolytics for postoperative bowel contractions

SIR,—I am grateful to Dr J W H Watt for his comments and suggestions (10 April, p 901) concerning our letter about hyoscine butylbromide used as a spasmolytic for postoperative bowel contractions (13 March, p 646). I agree that a torn suture line directly due to prostigmine is probably not a common complication of bowel anastomosis, so any remedy must carry a low risk to the patient. One of the drugs that Dr Watt suggests, papaverine, does not do this.

About 20 years ago, and for other reasons, I used intravenous papaverine in doses of 10-40 mg during general anaesthesia but encountered the following complications. Tracheal intubation was more difficult because of failure of pharyngeal and laryngeal muscles to relax even with suxamethonium, haemorrhage was considerably increased, abdominal exposure and closure of the peritoneum were made more difficult because of an apparent failure of the transverse muscles of the abdomen to relax, and reactionary haemorrhage and haematomas were common.

These effects were reduced but not abolished by intramuscular injection. It would seem that despite its theoretical advantages papaverine should not be used as an intestinal spasmolytic after abdominal surgery.

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Assessment of results of surgery

SIR,—Patients' assessment of their symptoms by linear analogue techniques, although appropriate in some situations, such as the assessment of postoperative pain, is not a suitable instru-

ment in the outpatient clinic as described by Mr R Hall and others (3 April, p 814).

In this study patients were asked to rate their own postoperative status on a linear scale ranging from "awful" to "perfect." There are intrinsic biases in this: (1) patients find it difficult to admit that an operation has done them harm because this implies blame on their surgeon; (2) it allows patients to please the surgeon by stating their condition to be "perfect." These biases may be sufficient to explain the tendency of patients who have suffered less than perfect operations to class the result as perfect.

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Iatrogenic gall stones

SIR,—I must take issue with your leading article on this subject (10 April, p 859). You infer that risk of gall stones should make the physician wary of prescribing oral contraceptives. By means of our feature card morbidity recording system I have determined that of the 9000 patients in this practice 474 are on oral contraceptives and not one of these presented with gall stones during the year ending 1 March 1976. Many of these women have been on the pill for more than 10 years.

As you state, "other methods for preventing pregnancy are available," but none combines the merits of effectiveness, reversibility, and convenience. A good deal more evidence than exists at present of risk of gall stones will need to be produced before sexually active women whose family is not yet complete should be denied the peace of mind which the pill usually brings.

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Metronidazole in treatment of empyema

SIR,—Little information is available at present on the penetration of systemic antibiotics into empyemas and we can find no reference on metronidazole in this context. This is perhaps surprising as in one recent study of 83 patients anaerobic bacteria were recovered from 76% of cases (these were the exclusive isolates in 35%)¹ and metronidazole has been increasingly recognised for its role in dealing with anaerobic organisms.² Being a relatively non-toxic antibiotic, well absorbed when given by mouth, we feel its use in empyemas is worthy of consideration. We would like to report our experience with this drug.

An 81-year-old man was admitted with right middle lobe pneumonitis. He subsequently developed a right-sided empyema which was drained with an intercostal tube. An anaerobic bacteroides organism particularly sensitive to metronidazole and also to clindamycin was cultured from the pus. Metronidazole 400 mg and clindamycin 300 mg were given orally six-hourly and the patient made a good recovery. A sample from the intercostal drain taken 3½ days after starting this regimen showed a metronidazole concentration of 24.2 µg/ml. The minimum inhibitory and bactericidal concentrations of metronidazole against *Bacteroides fragilis* isolated from clinical material, as determined by Whelan and Hale,³ were almost identical in several types of

abscess and varied from 0.7 to 1.2 $\mu\text{g/ml}$. This suggests a very effective level in the empyema drainage fluid. Unfortunately, our earlier samples were destroyed before assaying, but we feel that even this isolated assay may be of interest to other physicians faced with similar problems.

We would like to thank May and Baker Ltd for their help in assaying the drug.

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¹ Bartlett, J G, *et al*, *Lancet*, 1974, **1**, 338.

² Ingham, H R, *et al*, *Journal of Antimicrobial Chemotherapy*, 1975, **1**, 355.

³ Whelan, J P F, and Hale, J H, *Journal of Clinical Pathology*, 1973, **26**, 393.

Treatment of diarrhoea in childhood

SIR,—Dr Geoffrey Hatcher (6 March, p 571) espouses certain treatment for children's diarrhoea no longer supported by recent investigations. Water, alone or as a 5% glucose solution, is unphysiological as an oral replacement solution because: (1) with loss of as little fluid as 3% of body weight (not clinically apparent) renal free water clearance is impaired and intake of solute-poor fluids will cause hyponatremia^{1 2} and (2) glucose tolerance is impaired in diarrhoeal disease.³ However, a 1-2% solution of glucose, when added to saline, base, and potassium, is well tolerated.^{3 4} Such a glucose-polyelectrolyte fluid should be the basis for salt and water restoration of diarrhoeal fluid deficits by mouth in children strong enough to drink.⁵ Glucose in excess, especially when unaccompanied by salt, is malabsorbed⁷ and can lead to hypernatremia.⁸

Opiates and codeine should not be used even for "symptomatic value" in dysentery as they are certain to make the patient considerably more ill by retarding the expulsion of invasive organisms.⁸ Such drugs can also cause sequestration of stool in the bowel, temporarily masking the degree of fluid loss.

Absorbable antimicrobials to which shigella organisms are sensitive most certainly shorten both clinical illness and duration of bacterial excretion, both in inpatients⁹ and in milder cases in outpatients.¹⁰ Dr Hatcher should reconsider his objections on this point as well.

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¹ Leaf, A, *New England Journal of Medicine*, 1962, **267**, 24.

² Kingston, M E, *Journal of Pediatrics*, 1973, **82**, 1073.

³ James, W P T, Drasar, B S, and Miller, C, *American Journal of Clinical Nutrition*, 1972, **25**, 564.

⁴ Moenginah, P A, *et al*, *Lancet*, 1975, **2**, 323.

⁵ *Lancet*, 1975, **1**, 79.

⁶ Schultz, S G, and Curran, P F, *Physiological Reviews*, 1970, **50**, 637.

⁷ Hirschhorn, N, *Lancet*, **2**, 1049.

⁸ Dupont, H L, and Hornick, R B, *Journal of the American Medical Association*, 1973, **226**, 1525.

⁹ Haltalin, K C, *et al*, *Journal of Pediatrics*, 1967, **70**, 970.

¹⁰ Haltalin, K C, *et al*, *American Journal of Diseases of Children*, 1972, **124**, 554.

Hazards of monocomponent insulins

SIR,—The interesting report by Drs A W Logie and J M Stowers (10 April, p 879) indicates the importance of initial reduction of insulin dosage when changing from bovine and porcine insulin to monocomponent insulin. It

is important to emphasise that a further reduction in the dosage of a monocomponent insulin preparation may be required a long time after the changeover, as the following case report illustrates.

A 56-year-old housewife with a long history of unstable insulin-dependent diabetes was admitted to hospital for diabetic restabilisation. Before admission she had been taking 60 U of beef soluble insulin in combination with 12 U of isophane insulin twice daily (144 U/day). Her diabetes was eventually stabilised after three weeks in hospital on a dose of 66 U of Semitard in the morning with 20 U of Semitard in the evening (a 40% reduction in insulin requirement). Four months after discharge she was readmitted unconscious in hypoglycaemic coma which responded rapidly to intravenous dextrose. For two weeks before this admission she had experienced minor hypoglycaemic episodes but had failed to seek medical advice. Her diabetes was eventually restabilised on 66 U of Semitard once daily (a further 23% reduction in insulin dosage).

This report indicates that a late fall in insulin dosage requirements may occur. A significant fall was apparent in this patient four months after the change to monocomponent insulin. The decrease in dosage requirement may result initially because of a difference in binding capacity between bovine insulin and monocomponent porcine insulin. Also the lack of antigenic impurities in monocomponent insulins render them less immunogenic,¹ and a further reduction in dosage requirement spread over a longer period of time may occur. Within a year it is possible to recognise a new equilibrium in anti-insulin IgG antibody levels and insulin needs in patients transferred to monocomponent insulins.²

It is therefore advisable to recommend stepwise reduction of insulin dosage as may be indicated by hypoglycaemic tendencies and frequent clinic attendances for at least one year after the introduction of monocomponent insulin.

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¹ Schlichtrull, J, *et al*, *Diabetes*, 1972, **21**, suppl 2, p 649.

² Andreani, D, *et al*, *Hormone and Metabolic Research*, 1974, **6**, 447.

Doppler ultrasound in diagnosis of deep vein thrombosis

SIR,—The useful evaluation by Dr Jeanette Meadway and her colleagues (6 December 1975, p 552) of Doppler ultrasound in the diagnosis of clinically suspected deep vein thrombosis (DVT) should be taken as a clear warning of the limitations of this method, which the authors are careful to emphasise. In their (experienced) hands the estimated sensitivity of the method is 73% and the specificity is 72%.¹ Examination of asymptomatic patients shows an even greater degree of inaccuracy. Using the method described by Dr Meadway and her colleagues we examined 197 patients daily after hip surgery by Doppler ultrasound. Ascending phlebography was performed when positive ultrasonic or clinical findings were present or on the 14th post-operative day. A total of 144 deep vein thrombi were demonstrated by phlebography in 117 cases. None of 112 isolated calf vein thrombi in 92 cases (20 bilateral) were detected by ultrasound, and of 32 thrombi involving the thigh veins, 14 were not detected. Eleven of the 18

thigh vein thrombi detected by ultrasound were examples of whole-leg vein thrombi. Clinical embolism occurred in seven cases (3.5%) and in no case did ultrasound contribute to the diagnosis. Phlebographic appearances indicate that positive ultrasonic findings occur only at or near the point of total venous occlusion and that loose, non-occlusive, but potentially lethal thrombi give negative findings.²

Similar results have been described previously³ and again more recently.⁴ They show that ultrasound has no place in the monitoring of asymptomatic patients at risk of venous thromboembolism. But Dr Meadway and her colleagues have shown that the false-negative rate in symptomatic patients is also unacceptably high. Taken together, these observations indicate that the use of transcutaneous Doppler ultrasound should, with advantage, be finally abandoned in the diagnosis of recent DVT in favour of other non-invasive techniques which provide a high degree of accuracy⁵⁻⁶ regardless of whether the thrombus is situated in the calf or thigh veins.

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¹ Armitage, P, *Statistical Methods in Medical Research*. Oxford and Edinburgh, Blackwell Scientific, 1971.

² Cooke, E D, MD Thesis, University of Dublin, 1976.

³ Milne, R M, *et al*, *Lancet*, 1971, **2**, 445.

⁴ Rickford, C R K, and Negus, D, *British Journal of Surgery*, 1975, **62**, 182.

⁵ Cooke, E D, and Pilcher, M F, *British Journal of Surgery*, 1974, **61**, 971.

⁶ Bergqvist, D, *et al*, *British Medical Journal*, 1975, **4**, 684.

⁷ Cooke, E D, *et al*, *Lancet*, 1975, **2**, 51.

In defence of the under-40s

SIR,—I am obliged to comment on the Personal View by Dr John S Bradshaw (27 March, p 767), in order to defend "most doctors under the age of 40" and also the English language. The article severely abuses both.

The essence of Dr Bradshaw's discourse seems to be that such doctors are ignorant of the English language (and thus by implication, of its usage) and describes us—for I am well within the age group he selects—as morons and cultural savages. I infer that this is what he was attempting to convey, but the article was written so badly, was so shrouded in false assumptions, was so poorly constructed, and displayed such a complete disregard for grammar and syntax as to require two or three wearisome and laboured readings before I could understand adequately what the author was trying to say. After my initial reaction of indignation had settled—the man could not after all be taken seriously—I wondered whether a paragraph or two might be worth sending to the "Pseuds' Corner" editor of *Private Eye*. On further reflection, however, I felt that, since you had evidently seen fit to publish such nonsense, you should receive an appropriate protest.

The article, criticising the ability of "most doctors under the age of 40" to understand or use the English language contains 17 clichés, four grammatical errors, seven words or phrases which convey no meaning, and one tautology, and while admitting to the invention of the word "iatroceptogenic" Dr Bradshaw unwittingly invents two more—"jugglery" and "medicobureaucrats." All three inventions can be expressed simply and in an easily