ment. Confusion has probably arisen because the box refers to patients assessed 30 minutes after initial treatment with inhaled or nebulised β agonist (where "see box" appears in the text), but, unfortunately, the box is printed before this and the preceding paragraph of text.

In the text we state clearly that if features of an acute severe attack are present this should be recognised, assessed, and managed as described earlier in the article and that the medical registrar or senior medical house officer should be contacted to admit the patient. We agree that a peak expiratory flow of less than 40% of the predicted or the patient's best value is an indication for high concentration oxygen, bronchodilator, and steroid treatment followed by management according to the guidelines and including measuring the arterial blood gas concentrations. Such treatment would normally be started by the accident and emergency medical and nursing staff, unless the department was so busy that the medical registrar or senior house officer had to be summoned immediately. We would not, however, request the presence of the anaesthetic registrar except on, fortunately rare, occasions when the patient is moribund or unconscious. We specified medical registrar or senior house officer because in many hospitals the duty medical officer is a senior house officer.

Doctors should always consider a pneumothorax when they see a patient with asthma because it is such a serious complication, and the more ill the patient the more important it is to rule out this particular complication. But few patients require chest radiography in the resuscitation room, and our guidelines put this particular investigation in what we believed to be the appropriate context.

Ventilation of patients with asthma is a complex undertaking and should be performed only by experts. The details of intermittent positive pressure ventilation in these patients were beyond the scope of our guidelines.

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Preimplantation genetic diagnosis

SIR,—In her report from the recent meeting held in Chicago Ms Gail McBride states that currently, workers in preimplantation genetic diagnosis are concentrating on biopsy either of blastomeres from the cleavage stage embryo or of the polar body from the oocyte.¹ She reports that it would, however, be preferable to perform preimplantation genetic diagnosis on the blastocyst, from which extraembryonic cells can be obtained. The Chicago meeting, however, seems to have given the impression that there is a serious problem with blastocyst stage biopsy—namely, that embryo transfer in humans is not successful beyond day 3, whereas blastocysts develop only five to six days after fertilisation.

This conclusion is incorrect. Firstly, the first pregnancy established after in vitro fertilisation resulted from embryo transfer at the blastocyst stage.² This pregnancy was ectopic, however, and when subsequent work led to successful pregnancies following transfer at the two to four cell stage (day 2) later stage transfer was abandoned. Secondly, considerable success has been achieved in in vitro fertilisation after transferring frozen-thawed blastocysts.³ Thirdly, in a preliminary study, we have established a series of successful pregnancies after transfer on day 5 after in vitro fertilisation.⁴

We consider that these data indicate that biopsy of blastocysts should not be dismissed as a potential approach to preimplantation genetic diagnosis. Indeed, the importance of this approach cannot be overemphasised, as to perform single gene

diagnosis with confidence, rather than merely sexing the conceptus, it will be essential to obtain more than one cell from the preimplantation embryo.

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Reformulation of injectable vitamin A

SIR,—I suggest that there are other lessons to be learnt from the paper of Dr P A McCormick and colleagues.¹ The authors imply that the reactions at the site of injection were due to hypervitaminosis. This could have been determined by measuring serum retinol concentrations. I suspect that the concentration was normal and that the absence of general phenomena points to the solubiliser or something else in the formulation being the culprit.

Over 20 years ago I drew attention to evidence showing that vitamin A in oil had extremely low bioavailability when injected into muscle and therefore should not be used in treating xerophthalmia.² The World Health Organisation subsequently advised the use only of a water dispersible form parenterally.³ The authors' previous practice of giving monthly injections of roughly 30 times the daily requirement of vitamin A is questionable as only 1% of it could be used by the body, according to the information supplied by Roche.

This also makes sense of results that puzzled Walt *et al*⁴ when night blindness in three of their patients with primary biliary cirrhosis responded to oral doses of 50 000 IU vitamin A after having proved resistant to 100 000 IU vitamin A suspended in oil and injected intramuscularly.

I hope that Dr McCormick and colleagues will revise their decision to give water soluble vitamin A 100 000 IU only four monthly. There is no reason to believe that cellular requirements for vitamin A are altered in primary biliary cirrhosis, and therefore 100 000 IU monthly of a 50% bioavailable preparation would not be excessive, with average requirements at about 3000 IU (or 1000 retinol equivalents) daily. The availability of the vitamins D and K preparations should also be sought and appropriate dosage calculated likewise. Finally, vitamin E was not mentioned, though patients with liver damage often develop the spinocerebellar syndromes.⁵

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- 1 McCormick PA, Hughes JE, Burroughs AK, McIntyre N. Reformulation of injectable vitamin A: potential problems. *BMJ* 1990;301:924. (20 October.)
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AUTHORS' REPLY,—Careful reading of our paper will show that we did not imply that the local

reactions were due to hypervitaminosis A. In fact we believe that the local reactions are most likely due to some other constituent of the reformulated medication, such as polyoxyl 40 hydrogenated castor oil (Cremophor RH).

We agree that the reformulated vitamin A is better than the old preparation, and we would have used it previously had it been available in this country. Our decision to give patients 100 000 IU intravenously every four months is an empirical one, and Dr McLaren may be right that we should increase the dose. In view of the particular problems in patients with primary biliary cirrhosis, however, we are unwilling to do this until we have more experience with this new preparation.

Clinical evidence of vitamin E deficiency is very rare in adults with chronic cholestasis.¹ We therefore do not routinely prescribe vitamin E but use it in patients with very low serum concentrations of vitamin E or signs of peripheral neuropathy.

In conclusion we would like to state that the main aim of our paper was not to issue cast iron recommendations on vitamin A supplementation but to highlight the large changes in bioavailability that may occur after changes in formulation of established drugs.

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- 1 Jeffrey GP, Muller DPR, Burroughs AK, *et al*. Vitamin E deficiency and its clinical significance in adults with primary biliary cirrhosis and other forms of chronic liver disease. *J Hepatol* 1987;4:307-17.

Do streptococci cause toxic shock?

SIR,—Dr Philip Anderson draws attention to the shock-like syndrome sometimes seen in association with group A streptococci,¹ but *Streptococcus pyogenes* is not the only Gram positive organism that can be associated with septic shock. In a recent epidemiological study of bacteraemia in the United Kingdom a third of the isolates were Gram positive, and death directly related to bacteraemia was commoner in patients infected with Gram positive organisms than in those infected with Gram negative organisms.²

It can be impossible to distinguish shock caused by Gram negative bacteria by observation, suggesting that there may be a final common pathway of tissue injury. As there is now strong evidence that tumour necrosis factor has a central role in mediating Gram negative (endotoxic) shock^{3,4} we investigated whether Gram positive bacteria could induce the factor's production from macrophages.

We selected 63 Gram positive bacteria, including *Staphylococcus aureus*, coagulase negative staphylococci, streptococci of groups A, B, and D, viridans streptococci, and *S pneumoniae*. They were chosen to include both blood culture isolates and commensal strains. Culture supernatants were prepared that were free of cell wall fragments and had no endotoxin contamination. These were incubated with human whole blood,⁵ and the amount of tumour necrosis factor produced was measured by enzyme linked immunosorbent assay (ELISA). We found that most supernatants induced production of tumour necrosis factor at a level roughly one third of that induced by a positive control strain of *Escherichia coli*. Interestingly, we found no correlation between production of the factor and conventional markers of pathogenicity. Blood culture isolates were not more potent inducers of the factor, nor was enterotoxin production in staphylococci associated with greater factor production.

These data suggest that tumour necrosis factor may contribute to the shock syndrome seen with