simpler explanation for enhancement of anti-D levels.

The published graph of variations of anti-D concentrations with time shows a rise commencing between days 5 and 7, a high peak value being achieved on day 14, with a subsequent slow fall. The pattern would fit that of a classical secondary immune response¹ due to an immunising stimulus (that is, maternal infusion of rhesus positive erythrocytes) around day 0. We suggest that the likely immunising factor was the amniocentesis and intrauterine transfusion performed on day 1.² The failure to detect fetal cells in the maternal bloodstream does not exclude the possibility of fetomaternal haemorrhage as such cells are rapidly cleared in the presence of potent anti-D.³ We therefore invite the authors to reconsider whether the interesting data that they quote on K-cell lytic potential and inhibition of lymphocyte transformation might represent facets of a well-co-ordinated immune response rather than initiating factors of that response.

The authors refer to their disappointing results of treating other cases and to their use of Rh-unselected fresh frozen plasma replacement therapy. We measured the amount of red cells present in 10 carefully prepared plasma packs prior to freezing. On average 0.06 ml of blood (at packed cell volume 0.45) was present per pack (range 0.005-0.25 ml). When a pack was frozen and thawed, 4% of the erythrocytes survived intact. If 20 donor plasmas are required for a four-litre exchange, as much as 0.05 ml of intact Rh-positive erythrocytes might be infused. Such a stimulus is capable of exciting an antibody response in a good antibody former.⁴

In an attempt to reduce the amount of donor material needed for albumin and immunoglobulin replacement during intensive plasmapheresis, we have explored, in a non-pregnant volunteer, the possibility of absorbing the patient's plasma with Rh D-positive cells to reduce the anti-D content, with subsequent use of the absorbed plasma as a replacement fluid. The absorbed plasma was centrifuged twice and filtered at 0.22 μ before reinfusion. The initial anti-D level of 27 IU/ml fell after five plasmaphereses of 1200 ml each to 14 IU/ml; this was followed by a rise within seven days to 104 IU/ml, falling within a further week to 65 IU/ml. We therefore conclude that even the stringent attempts described to remove all D-positive material from plasma were unsuccessful and that sufficient Rh D-positive cells, or stroma, or both, remained to produce a typical secondary immune response.

In conclusion, we believe that enhancement of anti-D levels can be avoided if invasive uterine procedures (amniocentesis and intra-uterine transfusions) are kept to the irreducible minimum and that only Rh-negative plasmas should be used for plasma exchange of this group of patients.

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¹ Roitt I. *Essential immunology*. Oxford: Blackwell Scientific Publications, 1977:3.

² Zipursky A, Pollack J, Chown B, Israels LG. *Lancet* 1963;ii:493-4.

³ Jandl JH, Jones AR, Castle WB. *J Clin Invest* 1957; 36:1428-59.

⁴ Jakobowicz R, Williams L, Silberman F. *Vox Sang* 1972;23:376-81.

*. We sent this letter to the authors, whose reply is printed below.—ED, *BMJ*.

SIR,—Following the submission of our recent paper (28 June, p 1569) we have evaluated the effects of plasma exchange on a further four patients with anti-D. In each of these patients a rise in anti-D was seen, commencing between days 5 and 7 and reaching a peak between days 10 and 14, despite continued plasma exchange. Anti-D levels could not be controlled by

plasma exchange in three of the five women, and they lost their babies owing to haemolytic disease of the newborn despite intrauterine transfusions. In the two cases where control of anti-D was achieved Rh(D)-negative babies were subsequently delivered. The rise in anti-D in these latter two patients could have occurred only as a result of the effects of plasma exchange. Inhibitory factors were not found in these patients' serum and we assume that Rh(D)-positive stroma was present in the fresh frozen plasma, and provided the necessary antigenic stimulus.

We therefore agree with Dr Wensley and others and with Drs D Tovey and E A E Robinson (personal communication) that anti-D levels may be boosted by Rh(D)-positive stroma. However, in the three cases where intrauterine death occurred the situation would appear to be more complex. The rise in anti-D could not be controlled by plasma exchange and it is interesting to note that plasma inhibitors of lymphocyte function were present. We would assume that Rh(D)-positive stroma (or amniocentesis) provided the necessary stimulus to anti-D production, but we would suggest that plasma exchange adversely affected the maternal control mechanisms, resulting in "escape" of antibody production and death of the Rh-positive fetuses.

It is interesting to note that the anamnestic rise in anti-D levels in the patient receiving "absorbed" plasma described by Dr Wensley and his colleagues was also associated with plasmapheresis.

The points made by Dr A C Newland and others (9 August, p 452) regarding the kinetics of anti-D production are highly relevant, and we took these into consideration when designing our plasma exchange protocol. Our aim was to undertake plasma exchange on a daily basis until the anti-D level was reduced to below 5 IU/ml (1 μ g/ml) since there is a higher risk of fetal mortality above this level.¹ The longer-term aim was to continue plasma exchanges at the appropriate interval to maintain the low level of anti-D. However, we have not been able to achieve this in practice, and would seriously doubt whether it could ever be achieved during the whole period of gestation.

Because of the active and selective transfer of IgG across the placenta we elected to exchange with fresh frozen plasma (FFP) rather than albumin (stable plasma protein solution (SPPS)) solution in an effort to maintain total IgG levels but reduce the IgG anti-D component. However, it is clear from our experience and that of others (Tovey and Robinson, personal communication) that long-term transfusion of large amounts of FFP is associated with unacceptable side effects and one is obliged to use SPPS during intensive plasma exchange.

We would agree with Dr Newland and his colleagues that in most of the reported series plasma exchange to remove anti-D could hardly be described as "intensive," and in our view the beneficial effects claimed for plasma exchange alone are as yet unproved.

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¹ Fraser ID, Tovey GH. In: Cash JD, ed. *Clinics in Haematology*, vol 5 (1). London: W B Saunders, 1976:149-63.

Pseudomonas ophthalmia neonatorum

SIR,—In their article on pseudomonas ophthalmia neonatorum (9 August, p 440) Dr Gaynor F Cole and others state that the commonest cause of "sticky eye" in babies is the staphylococcus.

In a study of 213 consecutive neonatal eye infections in a maternity unit in Ayrshire I found that although *Staphylococcus epidermidis* was the most frequent organism isolated, 46% of the specimens yielding this organism had no pus cells in the stained smear, suggesting normal conjunctival flora.¹ In my study I found that the organism most frequently associated with the presence of pus cells was *Streptococcus viridans*.

A previous study from Northwick Park Hospital, Middlesex, of 104 infants with conjunctivitis and 104 healthy neonates also showed that *Strep viridans* was the organism most frequently associated with conjunctivitis.²

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¹ McGill RET. *Communicable Diseases Scotland* 1979; 13(22):ix.

² Prentice MJ, Hutchison GR, Taylor-Robinson D. *Br J Ophthalmol* 1977;61:601-7.

Chlorpropamide-alcohol flushing in non-insulin-dependent diabetics

SIR,—As Drs A H Barnett and D A Pyke record further striking observations based on the chlorpropamide-alcohol flush in diabetics (26 July, p 261 and in a paper in the *Lancet*¹), some questions must be asked before diabetics too readily use it as a nostrum to predict their future health (statistically) or before economy-minded doctors apply it to the disposition of health care among diabetics.

The observations are cross-sectional in time, but used to predict the temporal course of disease. This implies a knowledge of what is "post" and what is "propter" in the associations they describe—firstly, between absence of chlorpropamide-alcohol flushing on the basis of a questionnaire and increased liability to recorded macroangiopathy among diabetics and, secondly, between indomethacin blockage of chlorpropamide-alcohol flushing and relative freedom from angiopathy among diabetics with chlorpropamide-alcohol flushing. Suppose that macroangiopathy is associated with loss of liability of skin blood flow, or with changed resting cheek temperature (which Köbberling and Weber² showed was closely associated with the increase in cheek temperature in chlorpropamide-alcohol flushing on reanalysis of the data of Leslie and Pyke,³ and which we have found an important predictor ($r=0.5$, $n=61$, $p<0.001$) of the increase in cheek temperature after intravenous injection of glucose).

Again, suppose that younger chlorpropamide-alcohol flushing-positive diabetics without clinical evidence of angiopathy and with relatively warmer cheeks have in operation a process affected by indomethacin, and so possibly involving prostaglandins, but that this process is not active when there is obvious vascular disease. We may be learning more about the effects of vascular disease on skin blood flow or the role of the skin in body temperature control than about chlorpropa-