antihaemophilic factor in West Germany were requested by a group of international experts on home care to present valid data on why their dosages for therapy appeared so high. It is unfortunate that they have not done so, especially in the light of a 1979 Council of Europe report, in which the authors state: "The results of providing data about the use of coagulation factors in haemophilia treatment in the Federal Republic [of Germany] was unfortunately very unsatisfactory. The directors of three of the most active centres preferred to be evasive to the questions or to give only incomplete generalised answers.... Due to lack of information, in particular from Austria, Germany and Italy this report must be regarded as incomplete. In view of the fact that therapeutic material is obtained from blood or plasma of volunteers and the virtually complete dependence of severe haemophiliacs on this material, withholding information must be deplored irrespective of reasons such as competition for available markets."[10]

At the West German level of consumption, which appears to indicate a higher than usual use of blood product without supporting medical or statistical evidence of efficacy, the United Kingdom would require between 106·7 million and 313·5 million factor VIII units per annum. Taking a "minimum realistic commercial price" of 7·5p per unit[11] the annual cost of this treatment would be between £8m for home therapy and £23·5m for all treatment including the management of patients with antibodies. The present estimate of cost in the United Kingdom with a comparable population is £3·75m for 50 million units.

These figures suggest that there has been the creation of an artificial market for blood products in West Germany, a suggestion endorsed in a recent investigation by the magazine *Stern*.[12] It is probable that inflated demand and costs, estimated at 10 times the UK level by *Stern*, continues to distort both the use and the cost of factor VIII, and therefore presumably of other blood products, in other parts of the world. Of particular concern to clinicians—though not perhaps to many patients, who will tend naturally to opt for high dosage—is the possibility that the persistent overprescription of products obtained from multidonor sources may result in a higher long-term incidence of harmful side-effects in the recipients.

The second feature of the blood product market to cause concern is the use of plasma obtained from donors in developing countries. That this practice can be excused by arguing that the purchase of plasma increases the standard of living of the donors concerned is fallacious, because it hinders the World Health Organisation's policy of encouraging the development of self-sufficiency in these countries. In addition to the widely publicised example of Nicaragua, I have been told of recent plasmapheresis for export in Belize, Brazil, Colombia, Haiti, Korea, Lesotho, Mexico, Panama, the Philippines, Puerto Rico, Thailand, and Taiwan. In these countries only the Travenol Centre in Puerto Rico and that run by the Belize Pharmaceuticals Company Limited come under United States Food and Drug Administration (FDA) regulations.[13] To my knowledge, no single manufacturer of commercial plasma products is yet self-sufficient in terms of source material, all companies being reliant on plasma brokers to some extent. Within the United States excellent facilities exist for the collection of plasma and what brokerage occurs is carefully monitored to comply with strict FDA rules. What happens outside the areas of FDA surveillance is anyone's guess.

Many people in this country, including my own patients, have every reason to be grateful for the generosity of donors in other countries and for the skill of FDA-supervised fractionators. However, I believe that it would be wrong for the Department of Health to extend its present dependence on industry at the expense of more direct involvement with blood collection from unpaid, voluntary donors. Higher prices for blood products would result (it is no coincidence that the price of factor VIII is lower in the United Kingdom and higher in West Germany than in most other European countries), and the eventual destruction of one of the only remaining totally voluntary blood donation services left in the world would follow.

I think that my colleagues in the National Blood Transfusion Service would agree that our previous failure to become self-sufficient should be reversed. But it must be realised that nothing can be achieved without considerable changes in our organisation for the collection and processing of blood, and in our attitudes to its optimum use. It will not be enough for Government to emulate the platitudes expressed by the Secretary of State at the DHSS in 1976, when we were told that self-sufficiency was expected in mid-1977. On that occasion Dr David Owen said, according to the DHSS press release, "Blood voluntarily and freely given by the healthy to those in need is a manifestation of the values which we should all strive to maintain in society." If members of the present Government concur with this view they should be prepared to fund the changes, and to support actively both voluntary blood collection and centralised and efficient management for plasma fractionation.

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[1] Jones P, Fearns M, Forbes C, Stuart J. *Br Med J* 1978;i:1447-50.
[2] Penner JA, Kelly PE, Bouthaugh M. *N Engl J Med* 1977;**297**:401.
[3] Ashenhurst JB, Langehennig PL, Seeler RA. *Blood* 1977;**50**:181-2.
[4] Ripa T, Scaraggi FA, Ciaverella N. *Blood* 1978;**51**: 763.
[5] Harris RI, Stuart J. *Lancet* 1979;i:93-4.
[6] Stirling ML, Prescott RJ. *Lancet* 1979;i:813-4.
[7] Aronstam A, Wassef M, Choudhury DP, Turk PM, McLellan DS. *Lancet* 1980;i:169-71.
[8] Allain JP. *Thromb Haemostas* 1979;**42**:825-31.
[9] Brackmann HH. *Scand J Haematol* 1980;**24**, suppl **35**:43.
[10] Council of Europe. *Report of the European Public Health Committee on the preparation and use of coagulation factors VIII and IX for transfusion.* CDSP (79) 52. Strasbourg: Council of Europe, 1979.
[11] Watt JG. *Lancet* 1979;ii:301.
[12] Herold D. *Stern* (Hamburg) January 1979; No 3: 94-100.
[13] Directory of FDA-licensed source plasma locations. *Plasma Quarterly*; February 1979.

SIR,—The paper by Professor John Stuart and others (10 May, p 1169) has highlighted some of the major benefits for haemophiliacs resulting from recent trends in the use of factor VIII. They point out some of the problems remaining and I should like to draw your attention to what I consider to be considerable problems concerning the supply of factor VIII, some of which I believe will be accentuated by the increasing trend of home therapy.

Both Biggs and Cash have estimated the requirements of factor VIII in the United Kingdom to be around 50 000 000 units per annum.[1 2] Both these authorities have based their calculations on the annual usage of factor VIII up to and including 1975. For reasons documented below, I believe this figure to be now a very serious underestimate of future requirements.

(1) An explosive growth in prophylaxis (negligible in 1975 in the United Kingdom) has taken place from 1976.[3] The use of prophylaxis has been shown substantially to increase the usage of factor VIII, two to four times the amount of factor VIII in current use being required for a prophylactic programme.[4]

(2) The number of patients on home therapy in the United Kingdom increased by one-third in 1976.[3] Rizza[5] has shown that patients on home therapy use 15% more factor VIII than those on hospital-based treatment. This increase in usage of material may be balanced out by the trend to lower dosages for early bleeds treated at home.[6] However, the 15% failure rate at low dosage,[6 7] which is not very different from the retransfusion rates for boys at Lord Mayor Treloar College,[8] cannot be ignored. As the majority of bleeds are into the knees, elbows, and ankles, it is disturbing to contemplate the effect of lowering the dose of factor VIII still further in the 15-20% of joint bleeds which would have failed to respond even to standard dosage. One must speculate that the arthropathy engendered by the increased amount of blood present for a longer period in these joints would generate chronic arthropathies, which, in their initial stages at least, would result in more frequent bleeding.

(2) The lengthening haemophiliac life span is likely to lead to a doubling of the haemophiliac population.[9] The leading of normal lives by haemophiliacs will result in the fathering of many more carriers and thus a second increment of increase in the haemophiliac population in two generations.[9]

(3) It is self evident that most haemophiliacs who were able to produce children in the past were likely to have been suffering from milder forms of the disease. Because the severity of the disease breeds true in families,[10] an improvement in survival and therefore of reproductive capacity is likely to bias the haemophiliac population to the severer forms. As the severest 20% of the haemophiliac population use 80% of the blood resources, this will have a considerable impact on demand of factor VIII in the future.

(4) The treatment of patients with inhibitors to factor VIII has changed in certain respects over the past four years. Patients with low inhibitor levels and low antibody response to treatment with factor VIII are now treated with high doses of factor VIII for almost all bleeds.[11] This group of patients is not mentioned in the recommendations from the same unit in 1976.[12]

It is apparent from my own experience that the National Health Service cannot provide more than a fraction of my needs for the treatment of 70 severe haemophiliacs. The shortfall is made up by the purchase of expensive commercial concentrates and it has been made plain to me that there will be pressures to cut the amount made available and in the forseeable future no prospect of any increase. If this situation is reflected nationwide, and I have no reason to believe that it is not, then the escalating requirement must shortly overtake the diminishing resources and create a major crisis in the expectations for haemophilia treatment.

I think it is essential that we recognise and

attempt to avert this approaching crisis. As it is apparent that the National Health Service facilities are incapable of processing enough of of the voluntary donations from this country, surely we should explore the possibility of commercially successful private industries fractionating the material for the National Health Service. This approach would provide a glimmer of hope in what otherwise seems a very gloomy prospect.

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[1] Biggs R. In: Biggs R, ed. *The treatment of haemophilia A and B and von Willebrand's disease*. Oxford: Blackwell Scientific Publications, 1978:89-109.
[2] Cash JD, Spencely M. *Br Med J* 1976;ii:682-4.
[3] Jones P, Fearns M, Forbes C, Stuart J. *Br Med J* 1978;i:1447-50.
[4] Aronstam A, Arblaster PG, Rainsford SG, *et al. Br J Haematol*, 1976;**33**:81-9.
[5] Rizza CR, Biggs R, Spooner R. In: Biggs R, ed. *The treatment of haemophilia A and B and von Willebrand's disease*. Oxford: Blackwell Scientific Publications, 1978:153-71.
[6] Harris RI, Stuart J. *Lancet* 1979;i:93-4.
[7] Stirling ML, Prescott RJ. *Lancet*, 1979;i:813-4.
[8] Aronstam A, McLellen DS, Turk P. *J Clin Pathol* 1979;**32**:927-30.
[9] Biggs R. *Br J Haematol* 1977;**35**:487-504.
[10] Macfarlane RG. In: Biggs R, Macfarlane RG, eds. *Treatment of haemophilia and other coagulation disorders*. Oxford: Blackwell Scientific Publications, 1966:1-29.
[11] Biggs R. In Biggs R, ed. *The treatment of haemophilia A and B and von Willebrand's disease*. Oxford: Blackwell Scientific Publications, 1978:181-202.
[12] Rizza CR. In: Biggs R, ed. *Human blood coagulation, haemostasis and thrombosis*. Oxford: Blackwell Scientific Publications, 1976:365-98.

Deaths from non-accidental injury in children

SIR,—Your correspondents Drs K T Farn and H B Valman (3 May, p 1145) appear to accept the Registrar General's annual figures for infantile homicidal deaths whereas there is a useful body of evidence that the annual number may be considerably higher than the 80 or so reported in recent years. In a prospective study[1] in a population of about 200 000, Dr J E Oliver and I obtained a rate of 0·1 per 1000 children under 4 years old per year, which was over 2% of all deaths in children in this age range. For England and Wales this rate would account for over 300 deaths a year, with a range within one standard error (about 70% of samples) from 31 to 526.

We were able to examine nearly all relevant records of a larger group of 10 deaths where we considered there was real doubt about the external cause. Of these, inquests were held in nine cases and conviction for infanticide or manslaughter were obtained in three. In another case the mother was acquitted of causing the death but convicted of cruelty to a person under 16 years; so that in only four of the 10 cases was there considered to be legal evidence of assault. Coroners' verdicts in the other five were either accidental death (three cases) or open (two cases). The diagnosis in all the accidental deaths was some variant of asphyxia caused by inhalation of gastric contents. In one of the open verdicts it was cerebral haemorrhage after fracture of skull and in the other cerebral haemorrhage after a tentorial tear. The diagnoses in the cases associated with convictions were bronchopneumonia and cerebral haemorrhage after fracture of skull, and asphyxia. The case leading to conviction for cruelty was diagnosed as asphyxia caused by inhalation of vomit. In the case in which there was no inquest the diagnosis on necropsy was acute bronchitis and this was certified by the coroner. Multiple bruising was noted in the medical record. Two deaths occurred in hospital and two babies were dead on arrival at hospital, none of these being associated with convictions for infanticide or manslaughter.

These findings seemed to indicate that where the cause of death was not overt violence (for example, by suffocation by a pillow) there is less chance of allegation of assault leading to trial, and not all cases of overt violence such as fracture of skull have this outcome. There are obviously great difficulties in obtaining adequate evidence and we concluded that there should be thorough investigation of deaths from intracranial haemorrhage associated with injury not clearly precluding assault and from asphyxia (whether or not caused by inhalation of vomit) occurring under 1 year of age (80% of our sample). Noting the external cause (the E code of the ICD) on the death certificate wherever possible would help to alert statistical analysts to the frequency of supposed accidental causes which stretch credibility, such as being dropped, falling down stairs, etc.

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[1] Baldwin JA, Oliver JE. *Br J Prev Soc Med* 1975;**29**:205-21.

Tuberculosis in patients having dialysis

SIR,—On 10 May (p 1186) we criticised the recommendations of your leading article (9 February, p 349) on the treatment of tuberculosis in dialysis patients. In answer to our criticisms, you queried our prediction that the half life of isoniazid in slow acetylators would be increased only from three to about four hours in renal failure and recommended once again that such patients should be treated with only 150 mg isoniazid a day. However, a subsequent review of the literature reveals that in those studies that employed specific chemical methods for estimating isoniazid the mean half life in slow acetylators averaged 4·9 hours in patients with renal failure, compared with 3·8 hours in the controls—an increase of 30%.[1-4] This accords with well-documented evidence that renal excretion is much less important than metabolism in the elimination of isoniazid.[5] The isoniazid half life of 17 hours in a single patient with renal failure cited in your reply is from the much-quoted study of Ogg *et al.*[6] Inspection of the isoniazid blood levels illustrated in fig 2 of their paper, however, shows that this estimate must be fallacious; we calculate that the half life was probably between five and eight hours. Even if half lives were increased occasionally to eight hours, there would be no substantial increase in isoniazid concentrations, and certainly not to dangerous levels, since daily dosage with as much as 15 mg/kg isoniazid has been shown to be well tolerated in patients with normal renal function.[7] Peripheral neuropathy can be prevented by giving vitamin B6. There is therefore no justification for giving renal failure patients less than the standard dose of 300 mg daily, particularly since 200 mg a day has been shown to be less efficacious.[8 9] Nor is there justification for insisting on plasma isoniazid estimations, which are demanding in equipment and skill.[10]

You then repeat your recommendation that if ethambutol is to be used for the treatment of renal failure patients it should be given at a daily dosage of 5 mg/kg, on grounds of convenience and on the assumption that satisfactory levels will eventually be reached prior to dialysis. However, even if the half life of ethambutol were prolonged to 24 hours, the peak levels attained would never reach those achieved with the routine daily dose of 15 mg/kg in normal patients and would fall far short of those achieved by the standard doses used for twice- or once-weekly treatment (45 and 90 mg/kg respectively). Our conviction that daily treatment with 5 mg/kg ethambutol would be inadequate is further strengthened by a recent investigation of the pharmacokinetics of ethambutol in renal failure in which a specific gas-liquid chromatography method was used; ethambutol half lives were found not to exceed 10 hours.[11]

We are also upbraided for suggesting that streptomycin might be used in place of ethambutol for combined treatment with isoniazid and rifampicin. Even if an intravenous line were unavailable, we doubt whether the chance of haematoma formation would be large if intramuscular injections were given six hours before the start of anticoagulation and dialysis. Ototoxicity is not likely to be a serious risk if correct dosage is used. Moreover, if we have to consider the potential consequences of overdosage, blindness due to ethambutol is more serious than streptomycin-induced vertigo. Finally, we believe that the practical difficulties of administering doses of streptomycin or ethambutol prior to dialysis have been exaggerated, since these drugs would normally be given only during the first two months of antituberculosis treatment, when most patients are likely to be hospitalised.

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[1] Bowersox DW, Winterbauer RH, Stewart GL, Orme B, Barron E. *N Engl J Med* 1973;**289**:84-7.
[2] Reidenberg MM, Shear L, Cohen RV. *Am Rev Resp Dis* 1973;**108**:1426-8.
[3] Larsson R, Karlsson E, Molin L. *Acta Med Scand* 1977;**201**:223-6.
[4] Molin L, Larsson R, Karlsson E. *Acta Med Scand* 1977;**201**:217-22.
[5] Weber WW, Hein DW. *Clin Pharmacokin* 1979;**4**:401-22.
[6] Ogg CS, Toseland PA, Cameron JS. *Br Med J* 1968;ii:283-4.
[7] Tuberculosis Chemotherapy Centre, Madras. *Bull Wld Hlth Org* 1963;**29**:457-81.
[8] Tuberculosis Chemotherapy Centre, Madras. *Bull Wld Hlth Org* 1960;**23**:535-85.
[9] East African and British Medical Research Councils. *Tubercle* 1963;**44**:301-33.
[10] Mitchison DA, Ellard GA. In: Reeves DS, Phillips I, Williams JD, Wise R, eds. *Laboratory methods in antimicrobial chemotherapy*. Edinburgh: Churchill Livingstone, 1978:244-8.
[11] Lee CS, Benet LZ. In: Florey K, ed. *Analytical profiles of drug substances*. New York: Academic Press 1978:**7**:232-49.

Contraindications to immunisation

SIR,—Dr H B Valman (3 May, p 1138) was brief, and so he could not help leaving things out. I would take issue with him, however, over some of his advice. For example:

(1) According to Dr Valman, family or personal history of allergy is not a contraindication to whooping-cough vaccination. According to Wellcome, history of severe allergy *is* a contraindication.

(2) Dr Valman advises that measles vaccine