CORRESPONDENCE

We may return unduly long letters to the author for shortening so that we can offer readers as wide a selection as possible. We receive so many letters each week that we have to omit some of them. Letters must be signed personally by all their authors. We cannot acknowledge their receipt unless a stamped addressed envelope or an international reply coupon is enclosed.

Correspondents should present their references in the Vancouver style (see examples in these columns). In particular, the names and initials of all authors must be given unless there are more than six, when only the first three should be given, followed by et al; and the first and last page numbers of articles and chapters should be included. Titles of papers are not, however, included in the correspondence section.

Factor VIII supply and demand

SIR,—At the recent meeting of the American Blood Resources Association (ABRA) in Arlington, Virginia, the president of Alpha Therapeutics reviewed international plasma resources with special reference to the fractionation capacity and sales of blood products in Europe. Using available figures, he considered France to be "ill served by its socialised blood service," the United Kingdom "as a disgrace to be included in a fourth world . . . an indictment of what happens in a socialised system," and West Germany, with a market "bigger than the rest of Europe combined," as "on the basis of blood component therapy doing the best job probably in the world." ABRA is to be congratulated for providing the forum for open debate on the collection, distribution, and use of blood products, and the time has come to invite comment from a wider audience.

In 1978 the world market for plasma products was estimated at $1000m, this figure excluding most of the developing world, the USSR, and China. A commodity market of this size, with its potential for continued growth as new and safer products are introduced and as the scale of treatment spreads, contains the obvious incentive on the part of industry to collect and sell as much material as possible. What concerns me as a prescriber is how this is being done, and I believe that there are two areas for concern. The first lies with the demand for plasma products, and with how this might be manipulated; the second lies in the possibilities for the exploitation of plasma donors in developing countries. The two products which are presently in most demand and which "drive" the plasma market are factor VIII concentrate for the treatment of haemophilia A and albumin. As I do not prescribe the latter I shall confine my remarks to factor VIII.

At the end of 1978, because of a continuing shortfall in supply from the National Blood Transfusion Service, over 50% of factor VIII used in the United Kingdom for home therapy in haemophilia A was imported,[1] a fact that should be of concern to all those who give blood regularly in the United Kingdom. Despite an overall rise due to the implementation of home therapy programmes and to more planned surgery, the use per individual patient per year has remained remarkably constant, patients on home therapy requiring on average about 24 000 VIII units annually. Without exception the directors of those centres with patients on home therapy prescribe routinely between 250 and 500 units (the contents of one or two vials) of factor VIII to be given early in the course of acute bleeding episodes. An inquiry in 1978 established that this relatively low-dose regimen was not dictated by the imposition of financial restraint on the prescribing habits of any director, and there is now considerable evidence of the efficacy of low-dose therapy for the majority of acute bleeding episodes.[2–8] Although there may well be reasons for increasing this dosage in individual patients, the clinical indications for doing so should be clear. One example is the use of prophylaxis, but even when this is applied as an alternate-day regimen it only accounts for around 50 000 factor VIII units per year, a figure in accord with contemporary practice in some major centres in the United States (P Levine, personal communication).

In contrast, in 1975 the average factor VIII consumption by 700 West German patients was 95 000 units per patient,[9] this figure including the haemostatic cover for approximately 68 operations and 18 patients with clotting factor antibodies. But 80 patients undergoing "intensive rehabilitation" in one centre used an average of 130 000 factor VIII units per patient per year.[9] The discrepancy in the figures for the United Kingdom and West Germany has never been explained, despite the fact that at a meeting in Bonn in 1977 those responsible for the prescription of

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