

first exposure to ultra-pure material after many exposures to intermediate purity product have failed to provoke such a response, raises again the question of altered immunogenicity of ultra-high purity concentrates.

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- 1 Ehrenforth S, Kreuz W, Scharer I, et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. *Lancet* 1992; 339: 594-98.
- 2 Peerlinck K, Arnout J, Gilles JG, et al. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurised factor VIII concentrate. *Thromb Haemostas* 1993; 69: 115-18.

SIR—Addiego et al report a high frequency of inhibitor development in haemophiliacs treated with low-purity and intermediate-purity factor VIII. Determinants of inhibitor development among haemophiliacs might include age, age at diagnosis, and amount and type of clotting factor VIII infused. Infection with HIV may also affect inhibitor development.<sup>1,2</sup> Data from the Italian registry of haemophilia support this hypothesis.

So far, 1366 severe (factor VIII <2 IU/dL) haemophilia A patients have been tested for antibodies to HIV and for the presence of inhibitor: inhibitor has been reported in 21% (170/808) of HIV-seronegative haemophiliacs, and in 9% (43/458) of HIV-seropositive haemophiliacs (prevalence odds ratio 2.7, 95% CI 1.8-3.8,  $p < 0.001$ ). These results show that the presence of HIV infection may be associated with a significantly low frequency of inhibitor to factor VIII because of the immune down-regulation associated with HIV/AIDS<sup>1,2</sup>

Therefore, reports of the evaluation of the frequency of inhibitor should also include information about HIV serological and clinical status, especially in the studies that tend to evaluate this aspect of haemophiliacs treated with low and intermediate purity factor VIII concentrates, which certainly in the past have transmitted HIV to some haemophiliacs.

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- 1 Ragni MV, Bontempo FA, Lewis JH. Disappearance of inhibitor to factor VIII in HIV-infected hemophiliacs with progression to AIDS or severe ARC. *Transfusion* 1989; 29: 447-49.
- 2 Bray GL, Kroner BL, Arkin S, et al. Loss of high-responder inhibitors in patients with severe hemophilia A and human immunodeficiency virus type 1 infection: a report from the multi-center hemophilia cohort study. *Am J Hematol* 1993; 42: 375-79.

SIR—Addiego and colleagues, in their discussion of their results, state that their data can serve to make meaningful comparisons with the frequency of inhibitor development in previously untreated patients given only recombinant or monoclonal-antibody-purified concentrates. From a comparison with the results of previous reports on these ultra-pure products, they conclude that the frequency of inhibitor development in patients treated with recombinant factor VIII is lower than in patients with products of lesser purity.

To establish the frequency of inhibitor development associated with a particular factor VIII product, one should study patients who were treated solely with that product. Baseline data for inhibitor development on low-purity products should therefore be obtained from patients who used only one low-purity product. Addiego's study is not suitable for future comparisons, since several products were used, both between and within patients.

We reported a frequency of 6.3% in a group of 48 patients with severe haemophilia A, analysed in a closely similar way to Addiego's patients but exclusively treated with locally produced cryoprecipitate.<sup>1</sup> Guérois et al<sup>2</sup> showed an identical incidence (3/48) in patients with severe haemophilia A treated only with Innovate (high purity, solvent-detergent treated).

Addiego and colleagues compare their results with those of studies on Kogenate and on Recombinate, two recombinant factor VIII preparations, in which frequencies of inhibitor development are 25%<sup>3</sup> and 19%,<sup>4</sup> respectively. They fail to mention the very short follow-up in these studies. In the Kogenate study, median follow-up was only 9 exposure days in the patients who developed inhibitors, and 7 for those who did not; in the Recombinate study it was 11 exposure days for both groups combined. Since a median implies that half the events occur before, and half after this period, one may expect almost a doubling of the reported number of inhibitor patients once the follow-up is extended. Obviously, these data on recombinant factor VIII are too preliminary to allow these kind of comparisons.

In addition, we have recently demonstrated that a particular intermediate-purity product is clearly immunogenic.<sup>5,6</sup> One explanation of the Addiego results could thus be that during the period analysed (1975-85) one or several of their intermediate-purity products was also immunogenic, but that this was not appreciated because this aspect was not systematically studied.

We feel that the statement on the use of these data for future comparisons is erroneous, and that the comparison with ultra-pure products is biased.

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- 1 Peerlinck K, Rosendaal FR, Vermynen J. Incidence of inhibitor development in a group of young hemophilia A patients treated exclusively with lyophilized cryoprecipitate. *Blood* 1993; 81: 3332-35.
- 2 Guérois C, Rothschild C, Laurian Y, et al. Incidence of inhibitors specific for Factors VIII or IX in severe hemophiliacs A and B only treated with very high purity FVIII or FIX concentrates. *Thromb Haemostas* 1993; 69: 852.
- 3 Lusher JM, Arkin S, Abildgaard CF, Schwartz RS, and the Kogenate Previously Untreated Patient Study Group. Recombinant factor VIII for the treatment of previously untreated patients with hemophilia A. *N Engl J Med* 1993; 328: 453-59.
- 4 Bray GL, Courter S, Lynes M, Lee M, Gomperts E, and the Recombinate Study Group. Safety, efficacy and inhibitor risk of recombinant factor VIII (Recombine<sup>®</sup>) in a cohort of previously untreated patients (PUPs) with severe hemophilia A. *Thromb Haemostas* 1993; 69: 1205.
- 5 Peerlinck K, Arnout J, Gilles JG, Saint-Remy JM, Vermynen J. A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. *Thromb Haemostas* 1993; 69: 115-18.
- 6 Rosendaal FR, Nieuwenhuis HK, van den Berg HM, et al. A sudden increase in factor VIII inhibitor development in multitransfused hemophilia A patients in The Netherlands. *Blood* 1993; 81: 2180-86.

## Ammonium In Intravenous albumin preparations

SIR—During our research on the pathogenesis of hepatic encephalopathy, we unexpectedly found that intravenous albumin preparations contain a significant amount of ammonium.

In an enzymic assay (glutamate dehydrogenase kit, Boehringer Mannheim) and with the Blood Ammonia Checker II (Kyoto Daiichi Kagaku, Kyoto, Japan),<sup>1</sup> ammonium