Factor VIII is an expensive commodity when purchased on the international market. For reasons of economy, national self-respect and public health motives, many countries quite naturally wish to be self-sufficient from their own blood resources. Given a demand of about 30,000–60,000 IU per hemophiliac per year, or 2–4 IU per head of population per year; and given current yields of industrial-scale plasma processing between 120 and 250 IU per kg plasma, it is difficult to avoid the conclusion that factor VIII is now driving the national plasma and blood demand – not red cells, platelets or albumin. There must be a very high premium on improving the factor VIII coagulant yield from plasma, in order to save unnecessary collection of red cells which may be wasted.

In England, this realisation came at about the same time that our Medicines Inspectorate and the NBTS itself began taking a closer look at the way in which the NBTS separated and collected plasma for fractionation, the way in which cryoprecipitates were made and many aspects of production and quality control in large-scale processing at the national fractionation centres. Over the last four years, the production of cryoprecipitate in England and Wales has fallen off dramatically and the supply of plasma for fractionation has more than doubled. The average quality of that fresh frozen plasma has improved because it is now understood that the procurement of fresh frozen plasma is not a salvage operation; it must be carefully planned, costed and supported by the Transfusion Service.

One of the contributions the fractionators have helped to make is to look at the claims made for what makes plasma 'high quality' and to tell the Transfusion Centres which improvements might give the biggest return in terms of factor VIII yield. The Transfusion Centres know they will have returned to them factor VIII concentrate in proportion to the volume and quality of the plasma they send for fractionation and they are therefore keen to improve plasma quality at the lowest cost and disturbance to their existing practices.

What matters most economically, of course, is the yield of factor VIII delivered to the patient for every kilogram of FFP put into the system, but usually one has to draw inferences from comparisons made earlier in the process and even to see whether the yield is predictable from the factor VIII content of the plasma as it is frozen or as it goes into process. We will be talking mainly about the factor VIII content of plasma entering the process or the yield of concentrate after processing and freeze-drying (but before sampling for quality control). In a few cases it will be necessary to refer to data at the primary cryoprecipitate stage or before the finishing operations of sterile filtration dispensing and freeze-drying. Unless said otherwise, the process (1) used was the one established at Oxford seven years ago, or a minor variant of it (fig. 1). Different processing might promote the survival of a different selection of factor VIII molecules from the original plasma and no claims can be made for the universal application of our conclusions to different processes.
100-300 kg FFP

\[ \downarrow \] Thaw 0-2°C

Cryoprecipitate

- Extract in minimum vol. 0.02 M Tris, pH 7.0
- Absorb with Alhydrogel, centrifuge, filter

Adsorbed extract (4)

- Reduce pH to 6.6, temperature to 10°C

Cold supernatant

- Adjust citrate, NaCl, pH (5)
- Sterilise by 0.2 μm membrane filtration (6)
- Dispense and freeze-dry

Final product (7)

Figure 1. Oxford process for factor VIII concentrate of intermediate specific activity.

Over the years we have seen a number of changes in the standard plasma delivered to Oxford and to Elstree. Initial data were obtained from 5 litre packs, containing about 28 donations of 180 ml, frozen vertically in an approximately 2" layer between two plates cooled to about -60°C, reaching a core temperature of about -30°C in less than two hours. Some of the data were checked later against single donations frozen in PVC bags over about 15 or 20 minutes, in vapour phase of liquid nitrogen and opened at the fractionation centre by dipping the frozen packs in liquid nitrogen. More recently, the dominant input to Elstree has been a new polyolefin pack designed primarily for mechanised opening at the fractionation plant. This wedge-shaped pack is frozen in a variety of ways at the Transfusion Centres and is opened straight out of the -30°C freezer by a custom built machine. Recently, Oxford has been looking intensively at Haemonetics and other plasmapheresis plasma, arriving like conventional plasma in larger PVC bags and more recently in a new bag designed for semi-automated tear-down. Some may have seen prototypes of a more highly developed machine at PFC in Edinburgh, designed to tear open specially adapted satellite packs.

ANTICOAGULANTS

Perhaps the most convincing improvement we have seen is in the factor VIII content of plasma taken into CPD rather than ACD anticoagulant and the survival of that difference throughout processing. In the 5 litre packs of plasma, sampled just before fractionation; in the extract of cryoprecipitate from about 100 kg of plasma; and in the freeze dried product, the difference was highly significant (table 1). We checked that this plasma difference was maintained throughout a change-over from the 5 litre to PVC single donation packs. We attribute this difference to the inactivation of more factor VIII in the early stages of blood collection into a more acid anticoagulant medium (2). From time to time a Transfusion Centre has reverted to ACD in the hope of gaining some advantage in platelet recovery, and each time we have not needed to be told that they have made this change: the loss has been obvious from routine fractionation yields.