Letter to the Editor

The development of plasma-derived factor VIII concentrates

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In his articles on the history of the development of Factor VIII concentrates (1,2), Albert Farrugia referred to our work at the Protein Fractionation Centre (PFC) of the Scottish National Blood Transfusion Service. We would like to provide some additional information on our work, as this may assist those seeking to increase factor VIII yield.

The conditioning of frozen plasma

The process of warming frozen plasma prior to thawing, as described by Dr Farrugia (2), was introduced at PFC in the mid-1970s to aid the removal of plastic from frozen packs of plasma by holding –40 ℃ frozen plasma overnight at +4 ℃. The specific activity and solubility of the resultant cryoprecipitate were found to be increased by the procedure (3) which was termed "plasma conditioning" in a presentation at the 1983 World Federation of Hemophilia Congress (4). A specialist modular cold room was constructed at PFC for this purpose which could be programmed to provide rates of temperature increase and specified holding times such that production scale batches of plasma packs could be uniformly warmed from –40 ℃ to –10 ℃ over 10 hours and held at –10 ℃ prior to continuous thawing.

Continuous thawing of plasma

Continuous processing is used in the chemicals industry to increase the yield of sensitive components by minimising the time that they are exposed to harmful conditions. Application of this concept to the precipitation of proteins began to be studied independently in the late 1960s by Foster at University College London and by Watt at PFC, with the work at PFC being applied to plasma fractionation by the cold-ethanol (Cohn) method. The technology of Watt was revised by Foster and established into routine use at PFC in 1975, following which research was begun on the application of the concept to large scale cryoprecipitate production; with the development being disclosed in 1978 (5).

Continuous thawing of plasma was introduced into routine production at PFC in 1979, and was used to thaw all plasma at PFC until the centre ceased production in 2006. Following the introduction of continuous thawing, a resultant 57% increase in factor VIII yield (3), together with the removal of the process bottle-neck of batch thawing, contributed to Scotland becoming self-sufficient in the supply of factor VIII concentrate in the early 1980s. This also contributed to a 12-month stock of SNBTS factor VIII concentrate being established which, in turn, enabled a national inventory of 68 ℃ dry heat-treated concentrate to be produced as soon as evidence was available that HIV could be inactivated by this treatment.

The thaw-syphon technique for the preparation of blood bank cryoprecipitate, devised by Dr Mason (2), differed from continuous thawing of plasma in a number of respects. First, the difference in scale meant that the rate of thawing using the thaw-syphon technique was 0.3 litres per hour, compared with 200 litres per hour with large-scale continuous thawing at PFC. Secondly, with the thaw-syphon technique, the cryoprecipitate remains within the plastic bag throughout the thawing process making this a batch process from the perspective of factor VIII, leaving it vulnerable throughout the procedure, despite cryo-depleted

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plasma being continually removed to prevent over-heating within the bag (5). Although skilled research scientists were able to obtain high yields of factor VIII with the thaw-syphon technique, it was not sufficiently robust for the preparation of clinical cryoprecipitate in a busy blood bank and never achieved routine application in Scotland.

Control of ionised calcium and product formulation

In late-1980, it was observed at PFC that the addition of sodium citrate at an intermediate stage in the production of factor VIII concentrate caused a progressive loss of factor VIII activity during subsequent processing. The reduction or elimination of citrate proved unsuccessful and the alternative of adding calcium to maintain a constant level of ionised calcium was pursued. Results of this research (6) were first reported at a meeting of the British Society of Haematology in November 1982 (7). Information was shared with colleagues at the Plasma Fractionation Laboratory in Oxford and the technique was implemented in England in 1985 and in Scotland in 1986, to reduce loss of factor VIII activity in the manufacture of new Factor VIII concentrates, known respectively as 8Y and Z8 (8), both of which were dry heat treated for 72 hours at 80 ℃. Both concentrates proved to be free from transmission of hepatitis C virus as well as HIV. Patients who had not been previously treated with blood products were found to be free from immunological abnormalities after treatment with 8Y (9), despite its relative low degree of purity, suggesting that immunological abnormalities observed in people with haemophilia were caused by hepatitis C infection rather than a constituent of plasma which co-purifies with factor VIII in lower purity concentrates, such as transforming growth factor beta (1).

Similar considerations concerning the role of citrate were applied to plasma, with the concentration of citrate in anti-coagulants being reduced to half-strength, as described by Dr Farrugia (2). Although factor VIII activity was relatively stable in plasma collected in this manner and a high yield of factor VIII was obtained in cryoprecipitate, this was not reproduced in the preparation of factor VIII concentrate in large-volume trials (8). Possible reasons for this were identified which required further research to make manufacturing conditions more compatible with half strength citrate plasma (8). This work was deferred pending completion of studies on the compatibility of red cell concentrates with half-strength citrate anti-coagulant (10), by which time plasma-derived factor VIII concentrate had been largely replaced in Scotland by recombinant factor VIII and research on increasing factor VIII yield was no longer required.

In addition to controlling the level of ionised calcium, chemical additives were identified to prevent adsorption of factor VIII to surfaces during processing and in the final container, which are of particular relevance to the preparation of higher-purity concentrates (8). We preferred these additives to formulation in albumin, as the addition of albumin not only reduces the specific activity of factor VIII but also exposes recipients to many more donors.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the manuscript and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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