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Immunological Considerations

Physical or chemical treatment of plasma protein concentrates are potentially liable to result in immunological problems from two major sources.

A. Induction of Neoantigens

Particularly likely following chemical or enzymatic treatment of material.

A potential risk from two major standpoints;

- (i) Clinical reactions resulting from antibody formation to neoantigens occurring on repeated challenge. Early presentation would be anticipated.
- (ii) Risk of breakdown of tolerance to autologous protein antigens present within concentrate resulting in autoantibody formation. Potential for delayed effects operating against a wide range of antigens.

This aspect seems to have received attention from a number of groups and can be to some extent examined by animal immunisation and comparison of responses to native and treated preparations.

B. Increased Immunogenicity of Native Proteins

A similar but divergent problem not amenable to examination by animal immunisation. The theoretical aspect here is the documented effect of protein aggregation on the potentiation of protein immunogenicity. Soluble proteins are generally non-immunogenic, particularly by the intravenous route, whereas aggregated proteins are intensely immunogenic and indeed tolerance to autologous proteins can be broken by their aggregation. The mechanism is probably by increasing efficiency of antigen presentation. There is a considerable literature available on this aspect which indicates that heat aggregation is particularly effective in this regard. In animals, immunisation of heat aggregated gamma globulin (60°C) induces high titre rheumatoid factor production.

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Two areas are of importance with regard to factor VIII concentrates;

- (i) Possibility of autoantibody formation due to breaking of tolerance to a wide range of serum proteins aggregated in native form.
- (ii) Potential for enhanced immunogenicity of factor VIII when aggregated/denatured and delivered by the intravenous route.

In both cases appearance of autoantibodies may be delayed. In animal experimentation the effects are variable both in incidence and in time course and therefore lengthy clinical follow up may be required for effects to be observed.

A. G. Bird

Consultant Immunologist

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GB/LAT