PART ONE - THE USE OF ANTIHEMOPHILIC FACTOR (PORCINE) - HYATE:C IN THE TREATMENT OF ACQUIRED HEMOPHLILIA.

I. INTRODUCTION

Note for convenience of cross-reference copies of all papers cited are submitted as a separate bibliography volume.

a. Antihemophilic Factor (Porcine) - Hyate:C Background

The use of Antihemophilic Factor (Porcine) - Hyate:C in the treatment of congenital hemophilia patients with circulating antibodies to human factor VIII (so called inhibitor patients) is now well documented (Boylen et al 1984, Ciavarella et al 1984, Gatti and Mannucci 1984, Kernoff et al 1984, Briet et al 1985, Bona et al 1986, Ciavarella et al 1986).

This therapeutic concentrate of porcine Factor VIII:C has received Product Licence status in several countries and most relevant to this submission a Product Licence was granted in the United States of America in 1986 (Licence No. 1014).

The submission to the FDA for that Product Licence was supported by clinical data on the useage of Antihemophilic Factor (Porcine) - Hyate:C gathered under IND numbers 1679 and 2267.

Entry into the clinical study in the U.S.A. was restricted

to congenital hemophilia inhibitor patients and hence the licenced indication for Antihemophilic Factor (Porcine)-Hyate:C was also restricted to this category of patient.

It is well known, however, that hemophilia can arise spontaneously in previously non-hemophilic persons due to the generation of antibodies to Factor VIII:C in response to certain immunological disorders or disease states.

During the period of the clinical study of Antihemophilic Factor (Porcine) - Hyate:C in the U.S.A. (July 1982 - December 1986 IND 1679, IND 2267) a number of cases of acquired hemophilia were also treated using Antihemophilic Factor (Porcine) - Hyate:C. The responsibility for the use of the product in this indication was entirely that of the attending physician in whose judgement Antihemophilic Factor (Porcine) - Hyate:C was the most effective treatment option available. Full data records were obtained for these treatments and the case reports were submitted to the Office of Biologics.

This document compares the efficacy and safety of Antihemophilic Factor (Porcine) - Hyate:C in the above acquired cases with the use of Antihemophilic Factor (Porcine) - Hyate:C in congenital hemophilia patients. The clinical data from these treatments have already been presented in the Product Licence submission for Antihemophilic Factor (Porcine) - Hyate:C submitted in April 1985, Volume 5A (a copy of which is submitted with this

document).

Further evidence of clinical benefit is provided in Part Two of this document where a summary is given of the experience of the treatment of acquired hemophilia with Antihemophilic Factor (Porcine) - Hyate:C in the United Kingdom. Its use in both congenital and acquired hemophilia has been licenced there since 1984 (Product Licence No. 3070/0007).

b. Factor VIII Inhibitors In Non-Hemophilic Individuals

Although this condition is rare, with an incidence of approximately one case per 5,000,000 per year (Lottenberg et al 1987) it is certainly not insignificant compared with the number of hemophiliacs with high responding Factor VIII:C antibodies.

Furthermore the frequency of diagnosis may be low due to such patients presenting in non-specialist centers thus depressing the reported number of cases.

In a survey of 215 such patients (Green and Lechner 1981) the condition was documented to occur in post-partum women (7%) in patients with underlying autoimmune disease (18.5%) following drug induced hypersensitive reactions (6%) such as that against penicillin, in malignancy (6%) and skin and respiratory disorders (8.5%). Such cases also were found in patients with no apparent underlying disease (46%) generally in older age. (Percentage figures in parentheses relate to the incidence in the Green and Lechner survey).

It should also be noted that the spontaneous development of the Factor VIII antibody had serious consequences for the patient. Eighty seven percent experienced serious bleeding and in 22% death was attributed, directly or indirectly to the presence of the inhibitor. Such patients therefore are at severe risk of bleeding from trauma and surgery (Kitchens 1988). Also it has been noted that many non-hemophilic patients with inhibitors bleed more readily and from more sites simultaneously than do congenital hemophiliacs with inhibitors (Kasper and Ewing 1986) suggesting that spontaneously acquired inhibitors may have a broader effect than those present in congenital patients.

A number of reviews have been published on the subject of acquired hemophilia and these have been used to compile the overview of the subject given below (Shapiro and Hultin 1975, Green and Lechner 1981, Lottenberg et al 1987, Green 1987).

1. Post-Partum Women

Numerous cases have been reported of women who develop a specific inhibitor to Factor VIII within a week to one year of the delivery of a normal child. Characteristically both pregnancy and delivery appear to be normal and inhibitors have been documented following delivery of both male and female children and also following spontaneous abortion. In most cases there has been no underlying disorder and the

clinical presentation is often of a severe hemorrhage including pharyngeal bleeding and hemarthrosis. In general the inhibitor disappears spontaneously but this can be within a few months or as long as a few years. Once the antibody has disappeared subsequent pregnancies have not been reported to be associated with a recurrence of the inhibitor.

2. Patients With Underlying Disease or Drug Reaction

Acquired Factor VIII inhibitors have often been reported in individuals with underlying autoimmune disease states. These include Rheumatoid Arthritis, Systemic Lupus Erythematosus, and other less specific autoimmune syndromes. The clinical course in these patients is quite variable and seems to be related to the activity of the primary disease. Inhibitors have also been described in other disease states such as ulcerative colitis, enteritis, long standing asthma and skin diseases such as psoriasis and non- specific dermatitis. In several of these cases the patients had also been exposed to penicillin. This may have been instrumental in inducing the Factor VIII inhibitors since several episodes have been reported where inhibitors arose after penicillin treatment. There have also been reports of Factor VIII inhibitors arising after exposure to drugs, for example, sulfa, nitrofurazone and phenylbutazone. Inhibitors in this category have been found in both sexes and in a wide range of ages.

3. Patients With No Underlying Disease

A number of cases have been documented of patients undergoing a spontaneous production of Factor VIII inhibitor with no apparent related cause. In general such patients are elderly although there has been a case described of a 13 year old girl. Males and females are equally affected and the disease is variable sometimes remitting within a few months but often lasting for several years.

4. Properties of the Inhibitor

The acquired Factor VIII inhibitor in patients with no previous history of hemophilia appears to be an immunoglobulin, generally of the IgG class. Rare exceptions have been reported of IgA and IgM antibodies being associated with acquired hemophilia. The antibody light chain classes reported have been variable with no apparent correlation between light chain type and diagnostic category. Reported findings are different from light chain typing of hemophilic inhibitors, suggesting that antibodies arising in non-hemophilic individuals may be more hetrogeneous than those occuring in hemophilic individuals. The inhibitors in acquired hemophilia show species specificity and like hemophilic inhibitors cross react less with porcine Factor VIII than human Factor VIII. (See also page 39 of this submission).

In vitro non-hemophilic inhibitors generally neutralise Factor VIII in a more complex way than the majority of hemophilic antibodies. In many cases no amount of inhibitor plasma is capable of completely neutralising all the Factor VIII activity in incubation mixtures. The in vivo equivilant has been documented in a number of cases where circulating Factor VIII activity has been found to co-exist with significant titers of inhibitory activity. Such observations may suggest that non-hemophilic Factor VIII antibodies can occur in a much broader spectrum of affinities than those seen in hemophiliacs, or indeed that in some cases the non-hemophiliac antibody/Factor VIII complex itself retains some biological activity.

5. Therapy Options

The difficulty in managing a bleeding episode in acquired hemophilia patients is comparable with the management of congenital hemophiliacs with circulating inhibitors. The treatment of acute bleeding episodes or management of surgical intervention is in general approached by replacement therapy, initially with human Factor VIII. This approach may be successful where low affinity titer antibodies are present but in many cases acquired hemophiliacs seem to produce a high titer of antibody preventing the achievement of satisfactory circulating levels of infused Factor VIII. Also, as with congenital hemophilia, anamnesis may occur after Factor VIII exposure,

although the frequency of the occurrence of this response is not well defined.

Prothrombin complex concentrates, recently reviewed by Lusher 1987, may also be employed in the treatment of acquired hemophilia, but Lusher notes literature reports of failure to obtain hemostasis with those products and also questions whether the labelled units correlate well with hemostatic effectiveness. The risk of thrombogenicity of such products is pointed out and also several cases quoted documenting myocardial infarction in young inhibitor patients receiving large repetitive doses of prothrombin complex concentrates.

As with congenital hemophiliacs with inhibitors, plasmapheresis or extracorporeal removal of antibody using protein A is an option for the reduction of antibody titer in acquired hemophiliacs prior to replacement therapy. Insufficient data is available currently to evaluate this approach in spontaneous inhibitors.

Immunosuppresive drugs have been used in many cases in an attempt to reduce antibody titer, but it is difficult to draw conclusions regarding their efficacy because the course of the disease is in general unpredictable, and a variety of drugs and treatment regimes have been employed. However, it has been estimated that as many as 75% of non-hemophilic inhibitors show some benefit from immunosuppressive regimes and this rate is considerably higher than in the hemophilic

population.

It is probable that patients with underlying collagen-vascular disorders show the greatest response to immunosuppressive drugs and, in general, in patients without underlying disease such therapy is not usually successful.

It should be noted that while in the long term a reduction of the inhibitor by immunosuppressive therapy would be of benefit, such treatment is of no help during an acute hemorrhagic episode. In fact it may pose a potential danger since hematomas or surgical sites are liable to infection and immunosuppression would reduce the effectiveness of the patients natural response.

The treatment options available for Factor VIII inhibitor patients (both acquired and congenital) have been well reviewed by Bloom (1987) and Lusher (1987). See copies provided in the bibliography volume of this submission for further reference.

6. Potential Advantages for Treatment of Acquired Hemophilia With Porcine Factor VIII.

An important aspect to be considered with treatment of acquired hemophilia patients with human Factor VIII is the ever present risk of transmission of human viral diseases such as hepatitis and HIV. The relevance in these cases is acute since the vast majority of acquired inhibitor patients

will not have been previously exposed to human blood products.

For the indication of acquired hemophilia porcine Factor VIII in the form of Antihemophilic Factor (Porcine) - Hyate:C has a major advantage to qualify it for use as a primary treatment option. There is no clinical evidence to suggest that Antihemophilic Factor (Porcine) - Hyate:C has been associated with the transmission of any human viral conditions (Lusher 1987). Therefore patients treated with this product are not exposed to the risk of infection with human viral diseases. (Reference testimonial letters from Dr P Levine, Dr J Lusher and Dr C Kasper).

Additionally, the lower reported cross-reactivity of circulating anti-human Factor VIII with porcine Factor VIII means that successful treatments can be obtained with porcine Factor VIII even in the presence of titers of circulating antibody which prevent the use of human Factor VIII.

Therapy with porcine Factor VIII can also be controlled in the normal way that therapy with human Factor VIII would be, by conventional coagulation assay. This gives distinct advantages over the use of prothrombin complex concentrates where the ability to monitor the product in the blood stream is limited.