Conference Report

Factor VIII Concentrates: Current Issues and Future Prospects.
March 9-10, 1989, Bethesda, Maryland. Co-sponsored by FDA and NHLBI.
Delegates: R.S. Lane, J.K. Smith.

Evatt confirmed that, with the exception of an unfortunate 14 cases relating to a single product, no seroconversions to HIV had been seen in haemophiliacs, and none in 1500 patients prospectively followed by CTC since 1985 (2000 patient years, >100m iu, almost as good in total as the record of 8Y alone). The incidence of HIV-positive patients in the US ranged from 49-80% in the reporting centres; no lessons were drawn. There was an ominous increase in transmission to sexual partners in the 20-40 age group.

Mosley calculated that the number of haemophiliacs remaining HIV-negative was 21% for those treated with factor VIII, 48% for those treated with factor IX, and 81% for those treated with single-donor products. He believed that HIV was introduced into the US gay community in 1978, and that most haemophiliacs had been infected by 1982. Some of the influences selecting for gay donors were discussed.

Goedert pointed out that the incidence of HIV infection in recipients of factor IX was only 29% v. 77% for factor VIII, and he wondered why only 77% of those challenged had been infected. Was this resistance or protracted latency? AIDS/ARC was developing nine times slower in the 1-11 year age group than the 35-70 year group. (This was not invariably agreed by other speakers.)

Ludlam said that in the UK only 41% of factor VIII deficient patients (59% of severes) and 6% of factor IX deficient patients (11% of severes) had seroconverted, and confirmed that among the 135 patients who had progressed to AIDS within four years of infection, the rate among those <25 years was six times less than among those >45 years. Describing his Edinburgh cohort demonstrably infected by one batch of factor VIII, he said that the incidence of infection among those challenged correlated with previous annual dosage and with skin-test anergy. (In discussion, it was clear that he intended to imply that previous exposure to PFC concentrate, as opposed to cryoprecipitate, predisposed to infection. He found no confirmation of this from the audience (and I know none in the literature) and it may be interesting to probe the statistical basis of this inference before it takes root.)

Ragni believed that the period between HIV infection and development of AIDS in haemophiliacs was similar to that in the San Francisco gay community when corrected for age at seroconversion, the problems being worse with increasing age. The worst prognostic feature was T4 <100/mm^3. Haemophiliacs showed certain special clinical features such as ITP, septic arthritis and loss of IgG inhibitors.

Gomperts, studying three small cohorts receiving Haemofil M, had found no antibody to mouse protein after 3-18 months, by ELISA or immunoblot, and no circulating immune complexes (CIC). The previously-treated HIV-negative group showed no change in T4 over the study period, but their T4 starting levels were inversely proportional to ALT levels. He thought that NANBH infection might be responsible for changes in T4 or T4/T8 ratios. In discussion, this idea found much support from other speakers.

Gill had looked at two groups of patients, on Haemophil M and on a pasteurised IP concentrate, probably Cutter's. There was a very slow decline in CD4 levels and CMI skin test responsiveness, using either concentrate. This study was predominantly on HIV-positive patients and therefore has little relevance to us, but it tends to pull the rug from under Levine.

Hilgartner had looked at progression to AIDS in two groups, > or <21 years, and her abstract needs careful reading. Her percentage of seropositive factor IX-treated patients was very different from that given by Andes.

Tsoukas focussed on long term immune changes in HIV seronegative haemophiliacs, and found no progressive change in CD4 and no correlation between skin test response and concentrate usage. He would only give credence to skin tests if he had done the primary immunisation himself. There was no correlation of rate of infection with usage, and no other clinical dysfunction. There were marginal changes in HLA-DR + T cells and only very large increases in concentrate use were associated with decreases in response. He (and Gomperts) suggested that CIC were not important and no-one measured them anymore. In discussion, Ludlam quoted Frank Hill's evidence on transmission of TB, but no-one could raise other evidence of a change in resistance to infection with treatment.

Sullivan, an associate of Levine, had only 13 seronegative patients, but again found no difference in CD4 levels between controls and haemophiliacs treated with concentrate. He struggled to demonstrate a risk of "progressive immune attrition", but not very hard.

Gjerset compared 44 patients on factor VIII concentrates and 30 on cryo, all HIV negative, and with broadly similar usage rates. Absolute lymphocyte counts were normal except possibly in six patients on monoclonally purified VIII:C. There were no differences between the two groups in T4 and T8 counts (not even the rise in T8 seen by some others, and no IgG levels were measured). T4/T8 ratios fell roughly in parallel with usage, whether with concentrate or cryo. There was a small rise, among those on concentrate only, in CD8 + 12 + activated lymphocytes, but no difference in CD4 + 4B4 + (according to my notes). There were no significant differences between concentrate and cryo groups in four clinical signs and seven symptoms measured, and no relation to usage.

No-one disagreed with his suggestion that the neutral term "immune modulation" be substituted for "immunosuppression", which I took to mean that the changes observed with "increasing alloantigenic stimulus" could not be said yet to be detrimental or helpful to the patient.