Rejoinder to Dr. Fareed's Reply

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Dear Sir,

My attention has recently been drawn to a paper [1] which may also be unfamiliar to other participants in this controversy. It explores in general terms the relationship between biological potency (i.e., unitage) and therapeutic efficacy in a manner which is both relevant and cogent. While accepting the necessity of establishing a unitage system for 'biological' drugs, the authors demonstrate that potency must not be confused with efficacy and conclude that unitage 'cannot be very useful to the clinician in his estimate of a drug's efficacy'. From their papers it appears that Dr. Fareed and his colleagues reject this view; we believe that it remains a valid and necessary one.

The following are brief comments on passages correspondingly marked in the above reply by Dr. Fareed and colleagues to my original letter. If the work of Miles and Perry [1] is relevant, this is indicated.

A Heparin and insulin are examples [1]

B No such assumption was made [1].

C A gravimetric unit was seriously considered, but has evident disadvantages.

D It could be argued that this is equally true for heparin [1].

E It has always been so.

F A gravimetric unit is scarcely a better proposition: what are the alternatives? Confer ref. 1.

G But CY216 was singled out from the others in this respect.

H What evidence is there for this?

J I acknowledge an erroneous assumption, but confer my text.

K Dispersivity is usually expressed as weight average divided by number average; Novo may well take exception to the weight average given for their product.

L Our samples of CY216 and CY222 also have anhydromannitol end groups.

M Confer ref. 1.

N Compliance with what? It is not a low-molecular-weight heparin.

P We are not 'officials'.

R We agree entirely; our case in a nutshell!

S To my knowledge this has never been said or even implied.

T We believe 1 and 2 to be valid uses.

U The original investigation involved seven low-molecular-weight heparins from five essentially different preparative procedures, and the final choice was made from three, all differently prepared and all midrange in regard to the important parameter of molecular weight distribution.

V We disagree. Such differences as there are, are here exaggerated.

In figure 1 the assay data from table II in the paper by Barrowcliffe et al. [2] (see also 64

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ment with the results of Fareed et al. above) and shows no significant deviance. Øster-gaard et al. [4] have also concluded that, for use as potential antithrombotic drugs, 'the method of preparation seems to be of no or minor importance, at least if the molecular weight distributions of the products are similar'. Lot-to-lot variation may indeed be an important problem, but this will have to be controlled by the official agencies which permit clinical usage.

Fig. 1. Ratios of assay data for seven low-molecular-weight heparin samples plotted against the content of higher molecular weight material. For further explanations see text.

comment U above) are plotted (excluding that for the non-heparin sample B), in the form of two ratios, against the percentage of material in each sample with molecular weight greater than 7,500 [3]. Material below 2,500 had first been deducted as probably inactive, a procedure which improved the correlation coefficients slightly but not significantly. The degree of correlation permits a reasonable assumption that molecular weight distribution is a dominant factor in determining differences in potency between the assay systems used. Kabi 2165 is included (20% > 7,500, in reasonable agree-

References

Miles, A.A.; Perry, W.L.M.: Biological potency and its relation to therapeutic efficacy. Bull. Wild Hlth Org. 9: 1-14(1953).

Barrowcliffe, T.W.; Curtis, A.D.; Tomlinson, T.P.; Hubbard, A.R.; Johnson, E.A.; Thomas, D.P.: Standardization of low molecular weight heparins: a collaborative study. Thromb. Haemo-stasis 54:675-619 (1985).

Johnson, E.A.: An approach to a molecular weight calibration for low molecular weight heparins. Thromb. Res. 45: 675-680 (1987).

Østergaard, P.B.; Nilsson, B.; Bergqvist, D.; Hedner, U.; Pedersen, P.C.: The effect of low molecular weight heparin on experimental thrombosis and haemostasis – the influence of production method. Thromb. Res. 45: 739-749 (1987).