Comment on Two Papers by Dr. J. Fareed

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Dear Sir,

I would like to comment on the two papers by Fareed et al. [Haemostasis 18: suppl. 3, pp. 3-15, 33-47].

In the first paper [pp. 3-15] the text description of the high-performance liquid chromatography system differs in stationary phase, solvent, and detector from the description in the caption to figure 1, and it seems probable that the captions of figures 2 and 3 have been interchanged. In figure 5, the range of low-molecular-weight heparin (LMWH) potencies appears to be 80-125; in the text it is given as 15-120. For figure 7 the text description is unrelated to the results displayed. I must add that comprehension is made no easier by the arbitrary use of synonyms for the various LMWH samples (e.g., Fraxiparine and CY216).

Among the Conclusions to this paper is a reference to 'the superior clinical efficacy/safety performance of CY216, in contrast to other LMW heparins'. No evidence for this remarkably positive statement is provided.

In the second paper [pp. 33-47] I have concluded that figures 1-4 display results obtained as follows: Solutions of the LMWH standard and of the nine LMWH samples were made up in such a way that, on assay by 'an automated anti-Xa method acat (Dupont Company, Wilmington, Del.)' (not otherwise described or employed in this paper), they all had the same potency. The nine 'potency-adjusted' solutions were then assayed against that of the LMWH standard by four other procedures and the results displayed using scales on which the LMWH standard value is 1.0.

If this interpretation is correct (there is then an error in the caption of figure 2; anti-Xa in the second line should read anti-IIa), some of the results, notably in figures 2 and 4, correlate very poorly indeed with other published work. It is surely now generally accepted that in LMWH activated partial thromboplastin time (APTT) and anti-IIa potency are diminished relative to anti-Xa. Thus, an unfractionated heparin potency adjusted by an anti-Xa procedure against a LMW standard would be expected to have a markedly greater activity by APTT or anti-IIA than either the standard or other LMW samples. This is not the case in figures 2 and 4, and an even more surprising feature is the astonishingly high anti-IIa value given in figure 2 by CY222 which has the lowest mean

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molecular weight of them all. This result (unlike the others for anti-IIa) is strikingly at variance with the APTT one (fig. 4).

If data from the two papers are compared, some of the results are very difficult to reconcile. Figures 10-12 in the first paper and figures 9-11 in the second are likely to originate from the same series of experiments. One might expect a degree of parallelism, therefore, between the results for bioavailability and for cumulative response, and indeed this is so when measured by Heptest (1st paper, fig. 12; 2nd paper, fig. 11). It then becomes difficult to visualize time courses for blood activities by anti-IIa (1st paper, fig. 11; 2nd paper, fig. 10) which for two samples (3 and 5) give bioavailabilities which are probably not statistically different together with cumulative responses differing sixfold. It could be that legitimate data manipulation was used, but no account of any such procedure is given.

If some of the above criticisms appear to be trivial, a major defect of both papers is the total absence of any evidence for the statistical validity of the results. Anyone who has been involved in work of this kind must be well aware of problems, associated for example with non-parallelism in assays or with inherent variability of animals; the absence even of error bars in papers with such a polemical tone does nothing for the case they are intended to promote (cf. last but one paragraph of the Introduction). In this context, the reasons for the establishment of the International Standard for LMWH, and also

the recommendations for its use, have been misrepresented in a number of places; it is for example quite untrue to say [p. 34] that 'the NBSB recommended that only the anti-Xa actions should be considered while cross-referencing the LMWHs' or [p. 46] 'that the clinical performance of cross-referenced LMWHs would be equivalent to one another'. These two papers by Fareed et al. have in fact tended to confirm – within their above mentioned limitations – our original contention: that the behaviour of any one of a group of commercial LMWHs in relevant biological systems would in general be closer to that of other members of the group than it would be to ordinary heparin and that, therefore, estimates of potency, by any procedure, would show significantly better interlaboratory consistency using a LMWH standard than estimates using a standard of ordinary heparin.

It seems that Fareed et al. are in agreement with us as to the unsuitability in this context of ordinary heparin as a standard, but appear to believe that in consequence each manufacturer of LMWH must work out his own salvation without a standard. Grounds for rejecting this view have already appeared as published results from certain clinical trials.