PROBLEMS WITH THE INTERNATIONAL NORMALIZED RATIO

To the Editor:

In a recent letter to *Blood,* Hirsh called attention to the inadequacy of monitoring warfarin dosage by the prothrombin time assay (PT) as commonly performed in the United States.[1] The actual PT value may vary widely from laboratory to laboratory because the result is dependent on the "responsiveness" of the thromboplastin used for the test, and because the thromboplastin reagents distributed commercially by manufacturers in North America display a wide range of "responsiveness."[2,3] The need to reduce this variability led to the concept of the international normalized ratio (INR), a means of expressing the prothrombin ratio in a form that permits comparison with an international reference standard.[4]

Yet, even if every laboratory in the United States were to adopt the INR overnight, more work would be needed to achieve practical success. Hirsh mentioned "anecdotal reports of inaccurate calibration by manufacturers." Such reports are more than anecdotal: at least one recent example has been documented and reported in detail.[5] Hirsh also cited as major problems the wide range of international sensitivity index (ISI) values of thromboplastins distributed by North American manufacturers and the observation that the system does not work well with certain automatic clot detection systems. In our experience, even in a single laboratory using one reagent, a change of instruments led to INR mismatches.[5] This suggests that the existing equation for calculating INR is inadequate for dealing with the real-life variations in materials and methods used in American laboratories. Perhaps the problem can be solved by additional correction factors for these variables in the INR equation itself. Meanwhile, we agree with Hirsh's recommendations: (1) the range of variation in thromboplastin "responsiveness" should be more narrowly restricted by the manufacturers, and "responsiveness" should more closely resemble that of the international reference standard; and (2) an accurate ISI should be determined by the manufacturer for each anticipated reagent/instrument combination, including all of the common automated clot detection systems.

Until full confidence is established (or restored) in the INR system, it would also be helpful to provide a means of verifying the manufacturer's ISI value for each lot of thromboplastin, either through a central regulatory agency or by individual laboratories using a reference thromboplastin.

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To the Editor:

Dr Hirsh in his letter in the July 15 issue of *Blood,*[1] and in several previous publications, very clearly points out the problem of the variability in responsiveness of commercially available thromboplastin reagents to reduced levels of the vitamin K-dependent coagulation factors. There is no doubt that the need to report the results of the prothrombin time assay (PT) as an international normalized

ratio (INR) is critical to the adequate control of oral anticoagulation. It is therefore disturbing that so few laboratories in the United States have adopted this method of reporting PT results for patients receiving Warfarin.

I, however, would like to make one clarification in the formula used to calculate the INR. The INR is calculated as follows: INR = (observed PT ratio)^{C}. "C" is the valve representing the international sensitivity index (ISI) of the thromboplastin used in the assay. The observed PT ratio, as recommended by the International Council for Standardization in Haematology and the Inter national Committee for Thrombosis and Haemostasis,[2] is the ratio of the patient PT/mean normal PT. The denominator of this ratio is the "mean normal" PT and not the "control" PT as stated by Hirsh. Although these two valves are often similar, significant errors in the calculated INR can occur when they are not.

An acceptable level of accuracy in the determination of the mean normal PT is required for the derivation of the INR. The Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis, in its meeting of July 7, 1992, has recommended that the 95% confidence limits for the mean should not exceed ±5% of the mean. For most cases it is expected that this criterion can be met by determining the PT in 20 normal plasma samples. It was also recommended that this determination be performed for each new lot of thromboplastin and when there is a change in instrumentation.

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RESPONSE

I thank Dr P.A. Foster for his clarifying comments and agree with them. The control plasma is not the patients' pretreatment plasma, but the mean prothrombin time from pooled plasma obtained from 20 normal control subjects. I also agree that the determination should be repeated for each new thromboplastin and when there is a change in instrumentation.

I am pleased that the editors of *Blood* agree that the INR should be used to report PT results.

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