Activated protein C resistance in venous thrombosis

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the treatment groups (mean probability 0·12, 96% CI 0 04–0·18). 3 of the cases of eclampsia in group 3 were in the 7 women who received only anticonvulsant drugs. Abruption occurred with a similar frequency in all groups.

The hypothesis on which our study was based makes the assumption that lowering BP will reduce the occurrence of eclampsia and that adding an anticonvulsant will confer no extra benefit. No difference in progression to eclampsia was found between the two supervised study groups, which lends support to the hypothesis, although on the basis of the frequency with which eclampsia occurred in the study, this number of patients does not allow a definitive conclusion. It was not the intention of the study to see whether an anticonvulsant alone would be sufficient to prevent progression to eclampsia, but there was a disproportionately high occurrence of eclampsia in the small number of women in the standard treatment group who received only an anticonvulsant. 3 of these 7 women had eclampsia. Given the frequency of eclampsia among patients who received both antihypertensive and anticonvulsant medication in the standard treatment group, the probability of there being 3 cases of eclampsia in any group of 7 patients is less than 0 006. This finding provides further indirect support for our hypothesis and indicates that antihypertensive medication, with or without an anticonvulsant, is better than an anticonvulsant alone in preventing the progression to eclampsia. Based on the frequency of eclampsia in the standard treatment group (12%) and in the study groups, where effective antihypertensive treatment was given (5%), 240 patients would be required in groups 1 and 2 to confirm that adding an anticonvulsant does not further reduce the occurrence of eclampsia at $\alpha = 0\ 05$ and $\beta = 0\ 2$.

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Activated protein C resistance in venous thrombosis

SIR—Although we were pleased to read Tuddenham's commentary (Dec 18/25, p 1501) accompanying our paper on poor response to activated protein C (APC) and venous thrombosis, we feel that some of its phrasing might confuse the reader who is not familiar with the problems of hereditary thrombotic disease. Our research started seeking causes of thrombophilia. Nevertheless, our present study was not a study of patients with thrombophilia, but of consecutive patients with a first, objectively confirmed episode of deep-vein thrombosis. Patients with thrombophilia are a rare group, consisting of people with spontaneous recurrent, often familial, thrombosis at young age, among whom the burden of APC-resistance indeed amounts to 50%, as found by others[1,2] and mentioned in the commentary. Among our group of consecutive and unselected patients with a first episode of venous thrombosis, APC resistance was present in 21%. The difference is obviously due to the nature of the patient selection, but at the same time proves that APC resistance is not another rarity, but the single most important cause of thrombosis in average patients.

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Author's reply

SIR—As Koster and Rosendaal point out, the incidence of demonstrable coagulation defect in patients with venous thromboembolism depends strongly on case selection, a fact that I did not sufficiently emphasise in my commentary. The definition of thrombophilia varies from author to author but usually includes thrombosis under the age of 45, recurrence, and positive family history. The likelihood of identifying a defect increases with the stringency of the definition. The remarkable finding of the three published series is the very high incidence of APC resistance exceeding that of the previously identifiable defects put together. The overall incidence of APC resistance remains to be established in various other groups (arterial thrombosis, post-operative thrombosis, large segments of the normal population, ethnic subsets, &c), but meanwhile clinical pathologists and others will wish to add the test to their "thrombophilia screen" as soon as possible.

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Activated protein C resistance in deep-vein thrombosis

SIR—Koster and colleagues (Dec 18/25, p 1503) found a high prevalence (21%) of poor anticoagulant response to activated protein C (APC) in a series of unselected patients with deep-vein thrombosis (DVT) before the age of 70, and recommended the investigation of all patients with venous thrombosis for this abnormality.

We evaluated response to APC in patients with juvenile DVT. Frozen plasma samples (with normal activated partial thromboplastin time [APTT]), stored at −70°C, from 228 patients (males, age 12–45) with DVT before age 45, without underlying predisposing diseases (malignancy, nephrotic syndrome) were tested. Blood had been sampled at least 3 months after the single or last venous thromboembolic episode and 3 weeks after withdrawal of antithrombotic treatment. APC response was measured by APC resistance (Chromogenix, Sweden), which in our case proved to have an 8% between-assay variation coefficient (CV). The results were expressed as APC sensitivity ratio, obtained as follows: APTT(+APC)/APTT(−APC). Normal value for APC sensitivity ratio, obtained from the results of 40 healthy age-matched subjects, was greater than 1·99. In the patients examined, the results were quite similar to those of Koster et al, a poor response to APC being recorded in 49 of 228 samples (21 5%). However, in only 12 of the 24 who attended for repeat testing was the result confirmed. The remaining 12 showed normal APC sensitivity ratios; in all but 1 the difference from the first result was greater than the between-assay CV. Among the 49 cases with poor response to APC detected in the stored