Dr. Lamy that such rates are probably a much better reflection of current risk. These studies do not specify the rates for the subgroup with relevant carotid lesions, however, making the problem of finding appropriate "historical controls" even more vexing.

Fortunately, it appears that definitive resolution will become available in the next few years, when several large European and North American controlled studies are completed. Since aspirin treatment, apparently the best available medical therapy, does not seem to help women and only partially reduces the excess S + D rate in men, I hope fervently that surgery will be proven to be of value and that we will have a clear definition of the circumstances in which it is applicable.

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References

Thalamic Lesion Producing Ataxic Hemiparesis

To the Editor:

We read with great interest Dr. Murthy's letter regarding a patient with ataxic hemiparesis who had suffered a "thalamic" lesion. We find disturbing, however, that the lesion depicted by the computed tomogram (CT scan) is actually not localized in the thalamus. The CT scan shows a slice through the body of the lateral ventricles; the lateral walls of these are formed by the caudate nucleus, the corona radiata, and part of the internal capsule.2,3 The thalamus, on the other hand, serves mostly as the lateral boundary of the third ventricle, and only its most superior portion may abut the wall of the body of the lateral ventricles. In any case, this thalamic component would be posterior to where the lesion of Dr. Murthy's patient is shown.

Perhaps lower slices of the same CT scan, which could more clearly demonstrate thalamic involvement, might be shown. The previously reported cases to which Dr. Murthy refers actually show lesions that are lower than that shown in the CT scan presented by him. Although we don't doubt that thalamic lesions may give rise to the syndrome of ataxic hemiparesis, it is our opinion that the documentation of this lesion should be clarified. Enough uncertainty already surrounds the localization of lesions that can cause this syndrome, and it seems that the one questioned here is no different than some of the others previously described.

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References

Multicenter Trial of Hemodilution in Acute Ischemic Stroke

To the Editor:

Recently, the Scandinavian Stroke Study Group investigated the effects of hemodilution in a general stroke population. The study design, which had been previously reported, indicated that the major outcome measures were the proportion of institutionalized patients among the survivors at 3 months and the proportion of all patients entering the trial who were home at 3 months. A single-center trial was the source of background information, that is, the expected proportions in the control group.

There are major difficulties in interpreting the results of this study. First, analysis based on all patients enrolled in the trial is more appropriate than analysis based on survivors since the subgroup of survivors may be influenced by the treatment, leading to a selection bias. This is the case regardless of the fact that the treatment and control group mortality rates are similar and regardless of demonstrable similarity of the survivors in each group with respect to measured baseline characteristics. Second, sample size calculations for the second outcome measure were based on conservative estimates of the proportion of all patients entering the trial who would be at home at 3 months (see Figure 7 of Strand et al). From the single-center trial, 44% of the control group patients were at home at 3 months, with a 95% confidence interval of 30-58%. Using a more conservative estimate for the control group proportion, 45%, the power curve for a two-sided p <0.05 test of differences in proportions is given in Figure 1. It is clear from the power curve that differences of ≤15% would be very difficult to detect with a total sample size of 373 patients and maximum power of 0.80. Further, the power to

FIGURE 1. Power curve for two independent proportions.
detect the specific difference actually observed in this trial was 0.55. Therefore, the authors’ views regarding the risks of a Type II (β) error seeming small may not be universally held.

Lastly, the Scandinavian Stroke Study Group conducted interim analyses, which could have led to early stopping of the trial. The Scandinavian Stroke Study Group is to be applauded for including interim analyses in the conduct of the trial, but the Group should have discussed the interim analyses and their impact on the final analysis as a necessary part of the information conveyed to the audience.

I hope that this discussion will point out some of the difficulties in design, conduct, analysis, reporting, and interpretation of clinical trials.

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References

The following is in reply:
To the Editor:

When the Scandinavian hemodilution trial was designed, calculations of appropriate sample size were based on the results of our previous single-center trial. These prospective calculations have been presented in Stroke. If the difference in favor of the treatment had been as large in the multicenter as in the single-center trial, a total of 170 patients would have been sufficient if \( \alpha = 0.05 \) and \( 1 - \beta \) (power) = 0.80. These calculations were based on the proportion of survivors in institutional care 3 months after the stroke. If fatal cases were included, as suggested by Dr. Foulkes, 200–350 patients (depending on the expected effect of treatment) would have been needed if the same values for \( \alpha \) and \( 1 - \beta \) are applied. Against this background we decided to enter 400 patients.

Now that the final results of the trial are available, we know that we should have looked for a much smaller effect of hemodilution. Dr. Foulkes suggests that we should have designed a study documenting a 15% difference between treated and non-treated patients. Her remarks emphasize that our study was not designed to exclude a marginal effect of hemodilution in a favorable or an unfavorable direction.

As pointed out by Detsky and Sackett, “prospective” sample size calculations are incorrect once the trial is over; the actual data provided by the trial can then be used. Applying the tables published by these authors on the results of the Scandinavian hemodilution trial, approximately 200 patients were actually needed to detect a 25% reduction in the 3-month case fatality rate and approximately 300 to detect a 25% reduction in the proportion of patients in hospitals or nursing homes at 3 months. We included 393 patients.

Dr. Foulkes also suggests that interim analyses prompted us to terminate the trial earlier than was planned. When the study was designed, it was decided to enter 400 patients; seven fewer than that were eventually included.

Although the number of patients may seem very small to a biostatistician, our study was one of the largest (if not the largest) randomized trials of medical intervention in acute stroke at the time it was conducted. The recent Italian multicenter trial of hemodilution in acute stroke included 1,267 patients. The study protocol and the results were very similar to ours. An overview analysis, compiling all data available in randomized trials of hemodilution and plasma volume expander therapy in acute ischemic stroke, has now been initiated at the Clinical Trials Service Unit in Oxford, England. It is hoped that the total number of patients included in these analyses will be sufficient to meet even advanced biostatistical requirements.

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Thalamic lesion producing ataxic hemiparesis.
C R Gomez and S M Gomez

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/19/9/1181.2.citation

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