Assessment of Inter-Observer Differences
In The Italian Multicenter Study on Reversible Cerebral Ischemia

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SUMMARY A standardized protocol was used for duplicate examination by two neurologists of the clinical history and neurological signs in 55 patients with reversible cerebral ischemia. One trained examiner from each of eight clinical centres involved in the Italian Cooperative Study on reversible cerebral ischemia participated in this research. Duplicate examinations were compared in order to evaluate the percentage of agreement achieved in the responses. Several discrepancies relating to either historical data or neurological signs were detected. Possible causes of this disagreement are discussed. The inter-observer differences appear to be an important problem to be faced in cooperative studies on reversible ischemic attacks. The purpose of the study was to estimate these differences in the attempt to increase the degree of agreement by repeated training sessions and discussion between the different examiners. These efforts are needed to improve the quality of clinical investigations on reversible cerebral ischemia and to increase the validity of their results.

The clinical units are distributed in the Northern, Central and Southern Italian Regions. The design of the present investigation required that the neurologist of each centre be compared to the examiners of all other centres. The cross-comparisons of visiting and local neurologists were randomized according to a scheme providing that a total number of 28 visits was performed with two patients examined at each visit. Each clinical unit selected for each cross-examination two patients, not included in the general clinical research but presenting the same clinical features requested by its protocol. All patients had had reversible attacks of cerebral ischemia and had no mental disturbances impairing satisfactory responses to the questionnaire.

The longest interval of time between the last ischemic episode and the interview was 3 months. The overall duplicate examinations of two patients lasted 3 days according to the modality reported in table 1. Therefore each patient was examined twice from the visiting and the local neurologist within a 24-hour interval. On the whole, 56 patients were considered, but one patient is not included in this study because the forms were missing. The duplicate examinations were completely blind, i.e. completed forms were not shown to the other observer but sent directly to the Biostatistical Unit. The evaluation of discrepancy was related to the variables of clinical history and neurological examination included in the standardized questionnaire (table 2).

Some items of the clinical history deserve more details: the number of ischemic events was recorded according to the following scheduled responses: 1, 2, 3 to 5, and more than 5. The time features were derived...
from three items: time of the first episode—less than 2 weeks, less than 1 month, less than 3 months, less than 6 months, and more than 6 months; frequency—more than 1 a day, more than 1 a week, more than 1 a month and more than 1 a year; duration—5 minutes to 1 hour, 1 to 24 hours, and more than 24 hours. With regard to the type, multiple episodes were classified according to the duration and features of the neurological symptoms—all similar, one varying, all varying. Occasion was listed in seven categories: a) during sleep; b) at wake-up standing; c) during meals; d) during exercise; e) during excitement; f) during forced head movements; g) no occasion.

Each of the items of the neurological examination included two possible responses, positive or negative. In order to evaluate the degree of concordance, the index suggested by Goodman and Kruskal and termed "index of crude agreement" was used. This is the ratio between the number of subjects with agreement in responses and the total number of patients. By this method, discordance results from discrepant responses regardless of the magnitude of differences.

Results

Neurological history

Table 3 lists the variables of number, time features, type, and occasion of ischemic attacks. It is apparent that the best index of agreement concerns time of the first episode and duration, while it is lower than 50% with regard to frequency and type. Agreement related to the number of ischemic episodes was recorded in 54.5% of cases only. Furthermore, in 40% of cases we could not rely on the occasion of the clinical event as it was reported by the patient.

A second set of questions concerns the individual recall of neurological symptoms during episodes occurring in the past 12 months (table 4). If one considers motor symptoms, an agreement on positive recording was detected in 76.4% of cases. This agreement decreased to 63.8% with verbal symptoms, to 65.4% with visual symptoms and to 63.6% with sensory symptoms. Disagreement was not related only to complete omission by one of the two observers, but also to indication of a wrong side or a wrong part of the body.

With reference to the subsequent identification of the clinical territory, the information was in agreement between the two examiners in 65.4% of cases. It is to be mentioned that this variable was regularly discussed and recorded at the Central Office for patients entered into the general clinical study.

Neurological signs

With regard to the neurological examination, the variables are listed in table 5. An agreement on pathological recording of neck bruits at the same arterial site was achieved in 76.4% of cases. Identical responses were given in over 50% of cases when visual field defects, minor weakness, abnormalities of cranial nerves, and deep tendon reflexes were recorded. The agreement was even lower, below 50% of cases, on muscle tone, cerebellar, ophthalmoscopic, sensory signs and extensor plantar responses. Index of agreement was calculated from patients with one or both observers indicating a positive sign. In other words, agreement of both observers on "normal" examination was not considered.

Discussion

In long-term cooperative studies, the influence of interobserver discrepancy may be large both on the analysis of clinical data of patients at the time of entry and on the comparison between initial and follow-up assessments. This factor must be carefully evaluated because it may increase the "background noise" in the ultimate utilization of clinical data required for the interpretation of the results. In the study of ischemic cerebrovascular disease, the detection of new episodes during the follow-up of patients can be affected by inter-observer differences leading to erroneous conclusions in clinical therapeutic trials.
The differences may be due either to the interviewed patient or to the examiner. A recent study of neurological symptoms in 30 elderly patients revealed a discordance of 50% with reference to questions on faintness, lightheadedness or giddiness asked by the same interviewer on two occasions two months apart. To elucidate the role of discrepancies depending only on the examiner, a different area of study can be considered. In a paper of Cochrane and Garland, the reading of radiological findings of tuberculosis, carried out by radiologists in the United States and in United Kingdom, was compared in terms of the presence or absence of pathological signs on the same series of chest films. A discordance was found in 28.1% of cases.

It is reasonable that reversible cerebral ischemia with a history of short-lasting episodes and with no or minimal residual deficits may cause more discrepancies in clinical records than other diseases. The analysis of our results seems to confirm this assumption. It is surprising that disagreements were found to the same extent in the historical data, which are mostly "subjective," as in the neurological examination which, conversely, should be considered highly "objective."

Sisk et al., in a similar study on patients with reversible cerebral ischemia undergoing duplicate examination by two different neurologists, found a considerable amount of discrepancy on both neurological history and examination. They could determine, however, increased agreement in the neurological signs after carrying out a second set of cross-examinations following discussions which attempted to minimize differences between the two observers.

The results of the present study indicate that a few variables, regardless of whether they were historical or physical, had a poor degree of concordant responses. Particularly, the index of agreement was under 50% when frequency and type of episodes were recorded in clinical history and muscle tone, cerebellar, ophthalmoscopic, sensory and Babinski signs were detected in neurological examination. A percentage of agreement ranging between 56.4% and 69.1% was found in respect to the time of onset, duration and occasion of ischemic attacks, verbal, visual, and sensory symp-

<table>
<thead>
<tr>
<th>Signs</th>
<th>Index of agreement</th>
<th>Total no. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neck bruits</td>
<td>76.4</td>
<td>34</td>
</tr>
<tr>
<td>Visual field defects</td>
<td>91.7</td>
<td>12</td>
</tr>
<tr>
<td>Minor weakness</td>
<td>76.4</td>
<td>34</td>
</tr>
<tr>
<td>Deep tendon reflexes</td>
<td>63.6</td>
<td>33</td>
</tr>
<tr>
<td>Cranial nerves</td>
<td>56.4</td>
<td>16</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>43.6</td>
<td>16</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>37.5</td>
<td>16</td>
</tr>
<tr>
<td>Ophthalmoscopic</td>
<td>29.4</td>
<td>17</td>
</tr>
<tr>
<td>Sensory</td>
<td>25.0</td>
<td>12</td>
</tr>
<tr>
<td>Extensor plantar response</td>
<td>21.4</td>
<td>14</td>
</tr>
</tbody>
</table>

The World Health Organization has recently designed a clinical protocol for peripheral neuropathies. As a part of this protocol, eight neurologists from seven countries examined the same four diabetic patients. Among other findings, they graded the tendon jerks and their observations were then analyzed revealing an agreement averaging 52% for various reflexes.

In the light of these data, inter-observer discrepancy appears to be an important problem. The source of disagreement may be tentatively attributed to the individual interest of examiners toward particular features of attacks, symptoms or signs. The patients' recall of short-lasting episodes may be imperfect. Mild neurological signs may be equivocally classified as negative or positive responses. Poor motivation of patients and, to some extent, of examiners may be involved in any study as distinct from interest in decisions concerning the care and treatment of the patient. Lastly, differences in dialect, educational problems and social status related patients and examiners coming from different regions may play a role in determining discrepant results.

The purpose of this study was the evaluation of inter-observer discordance under our specific circumstances, with the final goal of increasing the index of agreement between the different examiners involved in the clinical research. Although a standardized protocol was used by trained neurologists, a need exists for continuous discussion between independent observers in the hope that discrepancies can be reduced. In our cooperative effort, we arranged several workshops in order to standardize the procedure of data collection and to minimize systematic biases. Similar measures appeared very useful in other studies, as was evidenced by Sisk et al. It is felt that by these means it will be possible to improve the quality of the clinical investigation and its results. It is suggested that these kinds of differences must be carefully estimated in multicenter studies on reversible cerebral ischemia, especially in evaluating prognosis and varying modalities of treatment.

Acknowledgement
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References

3. Fleiss JL: Measuring agreement between two judges on the presence or absence of a trait. Biometrics 31: 651-659, 1975
Dimethyl Sulfoxide (DMSO) and Glycerol, Hydroxyl Radical Scavengers, Impair Platelet Aggregation Within and Eliminate the Accompanying Vasodilation of, Injured Mouse Pial Arterioles*

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SUMMARY The hydroxyl radical scavengers dimethyl sulfoxide (DMSO) and glycerol were effective inhibitors of platelet aggregation in an in vivo mouse model of pial arteriolar injury. Aggregability was expressed in terms of the time required for a noxious stimulus (light + dye) to initiate aggregation. These drugs, given 1 hour before the injury, also eliminated the dilation which accompanied the damage. The same drugs failed to influence the constriction which accompanied an identical injury to mouse mesenteric arterioles, but again impaired platelet aggregation in the damaged mesenteric vessel. The data support the concept recently introduced by others, that, in the brain, hydroxyl radicals may mediate vascular damage and/or dilation accompanying the damage. The data also support the concept that platelet aggregation may be stimulated, directly or indirectly, by hydroxyl radicals. The effects of DMSO and glycerol in this study, irrespective of the molecular basis for the effects, may be relevant to the reported therapeutic benefit of these agents in cerebrovascular disease.

THE reported effects of dimethyl sulfoxide (DMSO) are protean and include the ability to impair platelet aggregation¹ ² and to reduce brain damage after occlusion of cerebral blood vessels perhaps by reducing cerebral edema.⁶ ⁷ The mechanisms by which DMSO exerts its actions are unknown, but might include its capacity to scavenge hydroxyl radicals,⁶ ⁸ a free radical species with potentially damaging effects. Since there are almost no studies of DMSO's action on platelet aggregation in vivo,¹ ³ particularly in cerebral blood vessels, and in view of reports concerning its beneficial action in cerebrovascular occlusion, it seemed essential to perform additional studies of DMSO's effects on the cerebral vasculature. This seemed particularly important in the light of renewed interest in the pathologic effects of free radicals⁶ and the failure of earlier workers to consider the free radical scavenging ability of DMSO when explaining their results. The following study not only assesses the ability of DMSO to impair platelet aggregation in injured cerebral microvessels, but also investigates the effects of DMSO on the alterations in vascular tone which accompany platelet aggregation in this particular model of microvascular injury. The action of DMSO in cerebral microvessels was compared with its action on mesenteric microvessels in the same model of injury, and with the action of glycerol, another scavenger of the hydroxyl radical,⁶ ¹⁰ that has also been reported to be of value in treating occlusive cerebrovascular disease.⁷ ⁸

Methods

Male ICR mice were anesthetized with urethan and either the surface vessels of the brain (pial vessels) or the mesenteric vessels exposed as previously reported.⁵ ¹⁰ The method of injuring the vessels and inducing platelet aggregation has been extensively described in earlier publications.⁶ ¹¹ Briefly stated, the vessels were observed with a Leitz Ultropak microscope that employs epi-illumination with either a tungsten or a filtered 200 W mercury lamp. The filters include a Leitz BG-12 exciter filter as well as heat and UV filters. The present studies employed a 10 x ocular and 22 x objective with an immersion attachment. With the mercury lamp the intensity of illumination at the focal plane with all filters in place was 23 × 10⁶ W/cm² when measured daily with a silicon diode detector and radiometric filter. The filtered light from

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