This is the latest in a provocative series of papers from Dr. Julio Cruz in São Paulo. He has made substantial contributions in forcing us to rethink our concepts of the role of hyperventilation and now mannitol in the treatment of patients with severe brain injury.

In this study, 44 adult patients with traumatic, nonpenetrating, severe, diffuse brain swelling were prospectively randomized to either a group receiving high-dose mannitol given ultra-early and fast at a dose of approximately 1.4 g/kg (23 patients) or to the control group of patients who received 0.7 g/kg (21 patients). Cruz, et al., note that there was a dramatic difference in the improvement in pupillary response in patients who received the higher dose of mannitol, and that this group had a much higher rate of favorable outcomes at 6 months (43%) compared with a 9.5% favorable outcome in the group receiving conventional mannitol therapy (p < 0.02).

The patients appeared to be relatively well matched with respect to computerized tomography findings and age. These results are clearly of substantial interest, but also raise questions about how reliable and valid are clinical studies that show very dramatic improvements in outcome when they are performed at only one institution. This does not mean the work of Dr. Cruz and his colleagues; rather it indicates that multicenter studies, such as those being conducted at present for novel pharmacological therapies, need to be applied to alternative dosing regimens for more traditional methodologies. Given the dramatic results reported here, it would not require a tremendous number of patients to learn whether the data reported by Cruz, et al., can be replicated.

A second point to be made is Dr. Cruz' discussion of the role of hypocapnia in the treatment of severe head injury. Although there have been cogent arguments that “optimized hyperventilation” is clearly beneficial and that ischemia is rare in severely head injured patients, this issue is still open to question. Although Cruz, et al., correctly cite the article by Diringer, et al.,1 which was recently published in the Journal of Neurosurgery, in which positron emission tomography scanning was used to study the cerebrovascular metabolic effects of hyperventilation, they report that Diringer, et al., failed to demonstrate the deleterious effect of reducing PCO2. Pickard and his group at Cambridge, who used diffusion-weighted imaging, have noted an increase in cytotoxic edema when hyperventilation is used (Pickard J, personal communication). Thus, one must consider carefully before concluding that hyperventilation has no deleterious effects on specific brain regions; more work must be done in this area. In addition, the need for another look at hyperventilation, which was in part condemned by the guidelines, should be addressed; this is probably also a study that should be conducted in a multicenter environment.

Dr. Cruz and colleagues have provided us with a series of stimulating and provocative observations that remain controversial. It is now time for the international neurosurgical community to test, in a multicenter study, some of his ideas to demonstrate whether the results are unique to São Paulo or have much more widespread application.

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RESPONSE: To the best of my knowledge, no one has ever published any effective treatment strategy for such a severely ill patient population (those with recent clinical signs of impending brain death), so that our paper is historically the first one. Under most conditions, these patients have just been used as organ donors, but our study has shown that it can be otherwise.

Indeed, among several novelties previously published, in 1998 we also first introduced in the pertinent literature a new concept of group matching according to only one intracranial lesion type.1 This elementary concept, however, has been ignored by others involved in prospective clinical trials, and all these trials were inconclusive because of that. Certainly, no matter how many centers and patients are involved, evaluating different therapies for consecutively admitted, unselected patients with several mixed lesion types represents basic lack of knowledge.

Contrary to the statement in this Editorial, there is no need for further studies involving our novel high-dose mannitol treatment proposition, because our study and control groups were extremely well matched with respect to the
main early parameters, according to our patient selection criteria. Under these conditions, 20 patients per group are enough for definitive conclusions to be drawn. In contrast, hundreds of patients per group may not be enough when mixed lesion types are evaluated. This explains, at least in part, the failure of most clinical trials, in contrast to our four successful ones.

My study from 1998,1 in which I demonstrated positive effects on clinical outcome of a novel proposed optimized hyperventilation regimen, involved the very largest patient population in this particular field of medicine, with no fewer than 353 properly selected patients in two extremely well matched groups as well. Improvement in clinical outcomes was remarkable for the group subjected to sustained optimized hyperventilation. Despite these striking clinical findings, in this Editorial the claim is made that a certain British study has disclosed increased cytotoxic edema caused by hypocapnia. On the contrary, among the several positive physiological effects of optimized hyperventilation (we have already published five of them), which far exceed the positive physiological effects of any other treatment strategy for these patients, the ability of hypocapnic optimization not only to reduce elevated intracranial pressure but also simultaneously to normalize the cerebral extraction of oxygen ([ICO2] simply the arteriojugular oxyhemoglobin saturation difference) makes it a most powerful therapeutic tool, because a normalized CEO2 indicates restoration of clinically beneficial coupling between global cerebral consumption of O2 and cerebral blood flow. Accordingly, there are no means of inducing edema formation, as mentioned, but quite the contrary.

Although our previous prospective controlled studies published in 1998,1 2001,2 and 20023 have shown the best mortality rates, ranging from 9 to 19%, with optimized hyperventilation as part of the treatment protocol, Polderman, et al.,4 reported the very highest mortality rate (76%) in contemporary neurotrauma history, insofar as traumatic intracranial hypertension is concerned. These authors used everything but optimized hyperventilation, including ventricular drainage, vasoressor drugs, frequent mannitol infusions, barbiturate therapy, and even hypothermia. These figures should be more than enough for the remaining few opponents of optimized hyperventilation.

Finally, this discussion clearly reveals that, contrary to the statement in this Editorial, there is nothing controversial in our several publications, only high-quality data from our most advanced bedside neuromonitoring and management, adopted for properly selected patients, who have received from us and our associates in several countries the most humanitarian and ethical dedication. We are sorry that a few others are still questioning what we have already made so clear.

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References