LETTER

To the Editor:

The study by Davidson et al. (1) concerning the treatment of multiple sclerosis (MS) with hyperbaric oxygen (HBO) raises some profound scientific and ethical issues. These investigators appear to manifest a marked unfamiliarity with the literature and its significance in helping design and execute human experiments and interpret data therefrom. Permit us to cite three examples: The first pertains to the incomplete reporting of methodology; the second, a more serious subject, involves the improper design and execution of human experiments, the interpretation of the data, and the ethics involved; the third involves the failure to quote relevant literature.

Davidson et al. provide no information concerning the equipment used in doing the magnetic resonance imaging (MRI) nor do they mention the nature of the slices they were examining. Yet in the extensive review of the subject of HBO and MS that we published in this journal (2) it was clearly pointed out that the data concerning the disappearance of small, newly forming lesions in MS were observed using equipment making 2.0-mm contiguous slices. It was suggested that the failure of others to note this phenomenon may be due, among other reasons, to the fact that they used equipment making 1.0-cm noncontiguous slices. In light of such existing criticism, one would expect investigators designing new experiments to take the necessary precautions and use appropriate equipment and provide the requisite information when publishing their results.

Magnetic resonance imaging data presented at the 1st Swiss Symposium on Hyperbaric Medicine (Basel, October 1986), with publication in said nonrefereenced proceedings, summarized our findings with a large series of cases. We certainly agree that peripheral lesions with no clinical significance form and disappear while the patients are undergoing HBO therapy. Patients, however, with lesions in the area of the pons, mid-brain, or cerebellum, with acute symptoms showed dramatic improvement even after a single exposure to HBO with reduction and/or disappearance of offending lesions.

Further, our review discussed in detail the methodological limitations of previous double-blind studies. Comments were made concerning the use of improper pressures and durations of exposure. It was pointed out clearly that 2.0 ATA is too high a pressure, especially in a monoplace chamber. When a too high pressure is coupled to a 90-min duration—which is too long an exposure even when using appropriate pressures—the treatment protocol cannot be justified. In fact, there are indications that such a pressure-duration treatment protocol may lead to worsening of the patient's condition. Indeed, the data of Davidson et al. reveal that 20% of their HBO-treated patients deteriorated whereas none of their air controls showed any deterioration. Deterioration was even suggested by their MRI.

Since Davidson et al. state that the "patients were interviewed and given an extensive consent form explaining the study and risks of treatment," we are concerned as to whether they informed their patients of their unjustifiable protocol and the attendant risks. Did they also provide their Institutional Review Board with the same information?

In light of the information currently available concerning the use of HBO in treatment of MS, one wonders about the ethics of designing and executing human experiments in which pressure-duration relationships are improper and hazardous to the health and welfare of the patient volunteers.

Davidson et al. state that "subject evaluation of benefit from these treatments was not systematically sought." We believe that such a cavalier attitude concerning the amassing of data from patient volunteers subjected to improper protocols to be unconscionable and raises serious questions as to what was their real motive in designing and executing this study. Yet, they find the casual comments from 12 of the patients, collected in a nonsystematic way, worthy of reporting. Such data are statistically meaningless, they not only lack completeness from the participants, they lack details concerning each of the categories in which some of the patients willingly provided information.

Davidson et al. state, in a somewhat surprised fashion, that there continues to be controversy concerning benefits obtained from using HBO. They cite as part of their evidence the initial negative Barnes et al. study of 1986, but they fail to mention the same investigators' final report in 1987 (3) in which long-term positive effects of HBO were reported. Nor do Davidson et al. acknowledge the extensive discussion we did concerning the nature of the controversy. If they had, they might have designed their experiment using proper exposure protocols and thereby avoided subjecting their patients to undue risks.

Clearly, the Davidson et al. study was an experiment designed to demonstrate the inadequacy of HBO as a therapautic modality for MS. It is easy to design and execute such experiments for any therapy for any disease, let alone MS. Poorly designed and executed studies reflecting attitudes as evidenced by Davidson et al. cast a negative reflection on the entire field of hyperbaric medicine. They also create unnecessary problems with third-party carriers.

Laudably, Davidson et al. felt that they could contribute to resolving the controversy by doing a randomized, double-blind, placebo-controlled study. Unfortunately, their study is markedly flawed. Instead of contributing to the resolution of the controversy, these investigators just added another layer of controversy.

In the initial data published in 1978-1980, a low-pressure protocol was utilized beginning at 1.25-1.5 ATA in a monoplace chamber. Several observations were made: 1) This is a dose-sensitive, long-term treatment; 2) this is not a cure for MS, but alters the natural history of the disease; 3) the patients must be picked, preferably below Kurtze category 5. Statistics from the 6000

MS-HBO patients in the ARMS study in the United Kingdom reaching their fifth year of treatment substantiate the original findings.

Schumacher has aptly stated, "a conclusion of benefit from therapy would rest on total prevention of exacerbation or further progression of the disease in the overwhelming majority of subjects over a two-year period." Any physician treating MS with 20 treatments of any therapautic intervention and drawing immediate conclusions thereof must be very cautious of any opinions formed or perhaps should not be treating MS patients.

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Note: Dr. Davidson has declined to respond.

References

1. Davidson JD, Davidson JA, Gado M. Magnetic resonance imaging in multiple solerosis treated with hyperbaric oxygen. J Hyperbaric Med 1989; 4:135–142.
2. Gottlieb SF, Neubauer RA. Multiple sclerosis: its etiology, pathogenesis, and therapeutics with emphasis on the controversial use of HBO. J Hyperbaric Med 1988; 3:143–164.
3. Barnes MP, Bates D, Cartlidge NEF, et al. Hyperbaric oxygen and multiple sclerosis: final results of a placebo-controlled, double-blind trial, J Neurol Neurosurg Psychiatry 1987; 50:1402–1406.

PROTOCOL FOR THE TREATMENT OF MULTIPLE SCLEROSIS WITH HYPERBARIC OXYGEN

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The use of pressurized oxygen in multiple sclerosis (MS) is analogous to insulin in the diabetic. That is, this is a dose-sensitive treatment and requires a long-term regimen. It is obvious that this is an attenuating mechanism rather than a curative procedure. Long-term patients have now been followed up to 16 years with no side effects from intermittent exposure to hyperbaric oxygen.

Although multistation chambers are quite satisfactory in the treatment of this disease, it is obviously easier to regulate the individual pressure in a monoplace chamber. When possible it is advisable that the physician talk to and examine the patient at least every other day during the course of the therapy to ascertain the optimum pressure. Once this is achieved, it remains the pressure of choice in the chronic progressive or stabilized MS patient. Alterations in pressure may be necessary during an acute exacerbation. The suggested pressures range from 1.25 to 1.5 to 2.0 ATA. the vast majority of

patients respond well in the range of 1.25 to 1.75 ATA; 2.0 ATA, however, is necessary pressure for a select few. The initial series should be continued as long as the patient is improving. Beginning MS patients at 2.0 ATA in a monoplace chamber forebodes trouble with poor results and possible harm to the patient. The average number of treatments given is 20 consecutive at 1 hour each, one to two daily. Some patients, however, have required as many as 80 initial exposures for stabilization and maximum improvement to occur. The protocol is 1.25 ATA for 4 treatments, 1.5 ATA for the next 8 treatments. If the patient is improving substantially at either one of these pressures, further change is not indicated. If there is no positive change by the 12th treatment, the patient is then moved to 1.75 ATA for the next 4 treatments. Again, if no change occurs, the patient is then taken to 2.0 ATA. If no clinical improvement has occurred at the end of 20 treatments, the initial series is stopped. It must be noted, however, that since oxygen therapy is cumulative, improvement may not take place until 2 or 3 weeks after cessation of the treatment. This is a most important period for observation to continue. Subsequent treatments are given depending on the patient's condition. Ideally, 1 to 2 treatments per week could be carried out with a repetition of the initial series of 20(+) treatments on an annual basis. In a large percentage of the patients, however, this is not mandatory and the average follow-up of about 1 treatment per month often suffices. Again, likened to insulin in diabetes, every patient is different and the medication must be titrated to the activity of the disease process.

In multiple sclerosis, an accurate evaluation of any therapeutic intervention cannot be made for at least 1 to 2 years. Schumacher's dictum for a treatment to be considered effective is that a large pecentage of the patients treated should be no worse at the end of 2 years.