HYPERBARIC OXYGEN THERAPY AND MULTIPLE SCLEROSIS

D.J.D. PERRINS[1] and P.B. JAMES[2]
[1]MS Therapy Centres, Bedford, UK, [2]Wolfson Hyperbaric Medicine Unit of Dundee, Ninewells Hospital and Medical School, Dundee, Scotland, UK

In his editorial last fall, Dr Jacoby [1] expressed the feeling that it was time to take a stand against the use of hyperbaric oxygen (HBO_2) treatment for patients with multiple sclerosis (MS). However, the Department of Health in the UK accepts low-pressure hyperbaric facilities for patients with multiple sclerosis and other neurological diseases. Over the past 20 years, a UK Charity has provided hyperbaric oxygen treatment in 62 centers for the amelioration of the symptoms of MS. Over 1.6 million patient sessions have been completed without a significant incident, which establishes the safety of the enterprise. A paper has been submitted to this journal (Perrins DJD and James PB) giving details of this experience. In contrast to Jacoby's position, in the same journal Bennett and Heard, [2] after reviewing the controlled trials of hyperbaric oxygen treatment in MS, do not close the matter and conclude that there is a case for further research. Our view is that the evidence, when reviewed in the context of the criteria suggested for the approval of conditions by the UHMS Hyperbaric Oxygen Committee, already supports the use of HBO_2 in the management of the disease.

1) Physiological reasons or models to account for possible effects;

The characteristic features of the typical MS lesion are blood-brain barrier disturbance and inflammation. Since first reported in 1991[3], several papers have reported the presence of lactic acid in MS lesions. The authors draw attention to edema limiting oxygen transport. Although it would be unethical to perform such an investigation in gas bubble related brain damage, we feel certain that lactate would be found. The lesions of multiple sclerosis are not in 'proximity' to vascular structures they are *peri venous* and associated with an acute disruption of the blood-brain barrier. This has been demonstrated by five imaging techniques, and may even precede the onset of symptoms. As an active tissue the blood-brain barrier is critically dependent on the availability of oxygen, and barrier permeability is reduced by the vasoconstriction induced by oxygen under hyperbaric conditions.

2) Existence of an animal model for the clinical situation, with data which demonstrate a positive effect on some outcome.

Decompression sickness produces demyelination and the comparison between DCS and MS which asserts that fat embolism is one cause of MS has not been refuted. [4] MRI has confirmed that both DCS and fat embolism may produce lesions in the cerebral white matter. DCS may also cause optic neuritis and ~~it~~ replicates the neuropathology of MS in the spinal cord. [5] Although large emboli in the CNS tend to cause infarction, microbubbles disrupt the venous blood-brain barrier. The putative animal model of MS, *Experimental Allergic Encephalitis* (*EAE*) involves blood brain barrier disturbance and research has shown that it can be prevented [6] and treated [7] by hyperbaric oxygenation.

3) Human studies, preferably randomized, controlled studies, which show significant benefits to patients for that indication. A few case reports or a case series is not usually enough to merit approval.

As stated by Bennett and Heard, the controlled studies of HBO_2 in MS did not follow the 1982 Lancet publication which gave the evidence for fat embolism as a cause of MS. [4] These studies followed publications which dated from 1970. However, Class 1 evidence is provided by the only properly conducted placebo controlled study of HBO_2 in MS and was published by Fischer *et al* in 1983. [8] It is the only trial of HBO_2T to match patients in pairs and then randomly allocate them to either treated or control groups. HBO_2. It is the only treatment ever to demonstrate improvement in chronic MS patients. The results are certainly not invalidated by the poor quality studies detailed by Bennett and Heard Fischer *et al* called for long-term studies, hence our recently submitted paper, and the investigation of the treatment of acute episodes. In his editorial, Jacoby does not refer to the Fischer study, citing only the final report of a UK study, which was not properly blinded and did not use a proper control exposure, matching or randomization. [9] These authors admitted causing 19 cases of severe ear barotrauma including a ruptured drum. However, they called for further studies after finding that the improvement in bladder function in the treated group following the twenty sessions lasted for six months and that there was less deterioration in the treated patients at the end of the year of follow-up.

Bennett and Heard correctly state that multiple areas of sclerosis are incurable. This is simply because sclerosis actually represents healing which, unfortunately, destroys function. The greatest justification for the use of oxygen under hyperbaric conditions is in the prevention of sclerosis with adequate treatment of the acute lesion but the average disease duration of the patients used in controlled studies of oxygen treatment was over 10 years. The disability resulting from the first attack of MS may be permanent [10] so the place of hyperbaric oxygenation, as in DCS, is at the onset of the disease. It should be noted that the HBO_2 studies quoted all took place long before beta interferon treatment was available. Beta interferon has not been shown to produce benefit and is prescribed to reduce the relapse rate in relapsing/remitting MS. Reducing the number of relapses from 3 to 2 over two years costs about $30,000. This is in marked contrast to the minimal cost of oxygen treatment, at least in the UK.

REFERENCES

1. Jacoby IJ. Hyperbaric oxygen therapy; multiple sclerosis, and unapproved indications: Taking a stand. Undersea Hyper Med 2001; 28:113-5.
2. Bennett M, Heard R. Treatment of multiple sclerosis with hyperbaric oxygen therapy. Undersea Hyper Med 2002;28:117-122.
3. Miller DH, Austin SJ, Connelly A, et al. Proton magnetic resonance spectroscopy of an acute and chronic lesion in multiple sclerosis. Lancet 1991;i:58-59.
4. James PB. Evidence for subacute fat embolism as the cause of multiple sclerosis. Lancet 1982;i:380-86.
5. Palmer AC, Calder IM, McCallum RI, Mastaglia FL. Spinal cord degeneration in a case of 'recovered' spinal decompression sickness. Br Med J 1981;283:888.
6. Warren S, Sacksteder MR, Thuning CA, Jacobs BB. Suppression of cell mediated immune responses by hyperbaric oxygen. Fed Proc. 1978; 37:560.
7. Prockop LD, Grasso RJ. Ameliorating effects of hyperbaric oxygenation on experimental allergic encepbalomyelitis. Brain Res Bull. 1978; 3:221-5.

8. Fischer BH, Marks T, Reich M. Hyperbaric oxygen for multiple sclerosis; a randomised, placebo controlled, doubled-blind study. N Eng J Med 1983;308:181-86.
9. 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;50:1402-6.
10. James PB. Monosclerosis or multiple sclerosis. Lancet 2002;359:1457.

RESPONSE OF DR. JACOBY TO JAMES AND PERRINS ON HIS EDITORIAL ABOUT MULTIPLE SCLEROSIS

The letter of James and Perrins has expressed objections to my editorial stand against the use of hyperbaric oxygen (HBO_2) therapy for multiple sclerosis (MS). The authors made a number of comments, which I will address herein.

The first argument for using HBO_2 therapy for MS is made by noting that the "Department of Health in the UK accepts low pressure hyperbaric facilities for patients with multiple sclerosis and other neurological diseases." Unfortunately, this is not a valid argument that HBO_2 therapy should be an indication for MS, but rather is an example of the "tail wagging the dog." Scientific reasoning should come first, before such expensive decisions are made. It would have been more prudent from a medical and cost viewpoint to await definitive studies of whether the modality actually worked for some forms of the disease. I am unfamiliar with why the UK Health Dept. in fact decided to approve such treatments when it did, but it was certainly premature, since the data did not provide the cause of MS or the efficacy of HBO_2. It is unfortunate the system was not used to study the effects of HBO_2 therapy, as the results of such large numbers of treatments may have answered many questions years ago.

The next arguments offered are classified as physiological arguments, based on disease modeling. The presence of lactic acid in plaques cannot alone be used to rationalize such treatments, since the MS plaque itself appears to be an end stage of scarring after failure to remyelinate, and treatment at that stage could not be expected to result in clinical improvement.

The issue of blood – brain barrier disruption is an interesting area of research, since antibody or mediator molecule penetration into the CSF is likely a major factor that permits the initiation of inflammatory changes within the CSF, resulting in demyelination**(1).** The timing of such changes in blood-brain barrier integrity might provide a window of opportunity for interventions of all sorts. But to make the leaps of logic from a pathophysiological process such as this to the use of HBO_2 to treat the disease MS in all its aspects, on a chronic basis, for years, is unwarranted. Certainly much more research is needed in this area.

The "fat-emboli" theory of causation of MS is not accepted currently. Modern theory of MS pathogenesis is that the disease is immune-mediated, and occurs in patients who are genetically susceptible. It also has areas of geographic prevalence around the world. The pathological processes leading to activation of inflammation resulting in demyelination remyelination, and ultimately, failure of remyelination are unknown. The pathological mechanisms of subsequent scarring and plaque formation in the CNS also remain unknown. Current therapy, which is based on better results than any of the MS studies using HBO_2, is based on contemporary immune theories of MS. The fat-emboli hypothesis proposed 20 years ago by Jones **(2)** is based largely on a few observations and leaps in logic with little supporting evidence. Since then, no studies have been published to support this hypothesis, and despite

much research on the pathophysiology of MS, no one has come up with evidence in further support of it. The burden of proof with respect to such a hypothesis falls on those who espouse it. In any event, HBO_2therapy is not currently approved for fat emboli, and the logic of using such a theory to treat MS patients is flawed.

The letter proposes that experimental allergic encephalitis (EAN) in the guinea pig, **(3)** is a model for MS, and thus the need for an animal model showing success of HBO_2 therapy has been fulfilled. The experimental EAN model produces demyelination using lyophilized guinea pig spinal cord, Freund's adjuvant, and heat-killed *Mycobacterium tuberculosis*. A more appropriate model of multiple sclerosis awaits better concepts of etiology, and would still only provide a strong rationale for devising clinical trials of HBO_2 therapy in humans. Furthermore, HBO_2 has been tested in human studies, and has failed to produce convincing evidence of efficacy. **(4)** From the perspective of human studies, the letter argues that the 1983 study by Fisher et al **(5)** is the only properly conducted placebo-controlled study of HBO_2 in MS, with multiple patient pairs, randomly allocated to either HBO_2 treatment or pressure controls. However, the study has several shortcomings, related to patient selection, confounding factors and statistical analysis. Responses to HBO_2 were said to be "short-lived." Furthermore, although the methods reports use of DSS, a functional systems scale and a fatigability scale, only the DSS data were reported. Two patients were included whose only symptoms were urinary frequency and urgency, which, in the absence of additional clinical data, could have been attributable to urinary tract infections.

In the later Barnes study (6), despite subjective improvement in reported bowel/bladder function in the oxygen group on the Kurtzke scale at 6 months, when objective urodynamic assessment was studied there were no improvements in the oxygen group, and two parameters deteriorated [bladder capacity and void flow rate], raising the question of the accuracy of MS studies if only subjective complaints are studied. The recommendations for studies proposed by Noseworthy et al include following patients out at least 3 years for follow up to identify biologically meaningful effects of treatment (1).

Although the letter argues that the place of treatment of HBO_2 is at the first attack of MS, because the deficit may be permanent, this is not the way HBO_2 is used by its practitioners. No study has really looked at the use of hyperbaric oxygen therapy in that fashion.

Finally, the author of the letter reports the "minimal cost' of oxygen treatment in the UK, although the cost of such treatments on a long-term basis for years cannot be inconsequential.

Newer and more effective forms of therapy for MS may make the HBO_2 debate moot. However, the letter has not brought any convincing arguments or evidence to support the widespread use of HBO_2 for the treatment of MS. I concur that studies should be encouraged, to try to elucidate the mechanism that brings about the breakdown of the blood-brain barrier and the long cascade of events that is manifests as MS. If there is a sub-group of patients with MS who might respond to HBO_2 alone, it will not be discovered by the kind of studies currently in the literature. Until better clinical studies are done, evidence that HBO_2 is an effective therapy for MS remains unconvincing, and thus it should remain unapproved.

Irving "Jake" Jacoby, MD, FACP, FACEP

Associate Director, Hyperbaric Medicine Center, University of California, San Diego, Medical Center, San Diego, CA Clinical Professor of Medicine and Surgery, University of California, San Diego, School of Medicine, La Jolla, CA

REFERENCES

1. Noseworthy JH, Lucchinetti C, Rodriguez M and Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938-952.
2. James P. Evidence for subacute fat embolism as the cause of multiple sclerosis. Lancet i.1982; 380-387.
3. Prockop LD and Grasso RJ. Ameliorating effects of hyperbaric oxygenation on experimental allergic encephalitis. Brain Res Bull 1978; 3:221-225.
4. Bennett M and Heard R. Treatment of multiple sclerosis with hyperbaric oxygen therapy:UHMS Position paper. Undersea and Hyperbaric Med 2002;28:117-122.
5. Fischer BH, Marks M, Reich T. Hyperbaric-oxygen treatment of multiple sclerosis: a randomized placebo-controlled, double blind study. New Engl J Med 1983; 308:181-186.
6. Barnes MP, Bates D, Cartlidge NEF, French JM and Shaw DA. Hyperbaric oxygen and multiple sclerosis: final results of a placebo-controlled, double-blind study. J Neurol Neurosurg Psych 1987; 50:1402-1206.
7. Ascherio A, Zhang SM, Hernan MA, Olek MJ, Coplan PM, Brodovicz K, and Walker AM. Hepatitis B vaccination and the risk of multiple sclerosis. N Engl J Med 2001; 344:327-332.
8. Gellin BG and Schaffner W. The risk of vaccination-the importance of negative studies. N Engl J Med 2001; 344:372-373.

LETTER TO THE EDITOR

In this issue of the *Journal*, Professors James and Perrins write of their positive clinical experience with hyperbaric oxygen (HBO_2) treatment of multiple sclerosis patients. Actually, I find Professors James and Perrins point attractive that hyperbaric oxygen may help multiple sclerosis patients over a long period to allow them to be maintained at a higher functional level. Obviously, for good science, this needs to be proved unequivocally.

Personal attacks about "neurologists" or certain other people do nothing to improve the plight of our patients with MS. Demyelinating disease is devastating. I have followed well over 1000 MS patients in 32+ years of clinical practice. They need help; we need good therapy; obviously a cure is still being sought! Attacking clinicians who care for these patients is not productive.

The risks of HBO_2 therapy are not an issue. All therapy has some "risk". However, ignoring the excellent autoimmune data on MS, along with the epidemiology information from Kurtzke, Hauser, et al, is wrong. The vascular vs autoimmune "discussion" of pathogenesis has been present at least since the 1950's (maybe before) and clearly autoimmune etiology to demyelinating processes is most likely. This is based on present pathologic and therapeutic data. To ignore this would be wrong.

Lactic acid or lactate present in MS lesions may indicate hypoxia or consequence of inflammatory process and damage. Oxidative/nitrosative stress is well defined in MS lesions and several anti-oxidants and anti-oxidant enzymes have been implicated in animal models of MS, as well as suggestion of benefit of anti-oxidants in Phase I clinical trials. To properly evaluate incremental therapies, outcome measures are essential that reliably assess all the parameters of

prognosis. At this time, all disability and outcome measures for multiple sclerosis have some limitation, even the EDSS, which measures primarily lower extremity and ambulatory ability and does not represent significantly the activities of daily living or cognitive end of multiple sclerosis problems.

Although DCS may share some pathologic characteristics with MS/EAE, it is not the same as MS clinically and the relevance of studying MS as a microembolic disease is physiologically unclear. DCS may cause peri-vascular inflammation or axonal injury and MRI changes do resemble MS, but many diseases other than multiple sclerosis have been known to have these findings also. Neurologists who see these patients know that many of the patients sent with multiple sclerosis with or without certain "characteristic" MRI changes, do not always have multiple sclerosis. Sarcoidosis and lupus vasculitis would be two obvious examples.

HBO_2 may help these patients even if we do not know how. But this must be proven using rigorous clinical research methods. HBO_2 therapy has been wrought with anecdotal reports, some of them mine, which do not prove treatment efficacy. No neurologist accepted β interferon therapy modalities without repeated control studies. This is what HBO_2 needs in order to become the universally accepted practice that is suggested by Professors James and Perrins.

Do more studies; let us have proof. The temporal profile of demyelinating disease is so variable that many, many patients are needed to demonstrate positive therapeutic results. But these patients need all of us to go for it!

E. Wayne Massey, M.D., F.A.C.P.