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HYPERBARIC OXYGEN FOR MULTIPLE SCLEROSIS

Philip James

The medical profession's response to the introduction of yet another therapy in multiple sclerosis is a scepticism conditioned by years of frustration in the search for a causative agent and an effective remedy.

To suggest that oxygen may be of help in multiple sclerosis (MS) would seem extremely farfetched, especially when the last 25 years have seen research effort into the immunological abnormality in MS, even though other diseases where the cause is known, for example neurosyphilis, produce similar changes. Over 47 studies of immunosuppression therapy, including several controlled trials, have failed to show clear evidence of benefit to patients.

January of this year saw a milestone in the history of MS with the publication of a successful double-blind, controlled trial.[1] The treatment group received oxygen under hyperbaric conditions. There was immediate improvement in 12 out of 17 of the treated group, contrasted with 1 out of 20 in the controls ($p<0.0001$).

Perhaps even more remarkable, there was stabilization of the 12 patients who had responded to the oxygen therapy over the subsequent year. Five maintained their improvement and none of the 12 had deteriorated to below the pre-treatment level. Of the five remaining patients in the treated group, who did not show objectively measurable improvement, only two showed deterioration over the following year. In contrast, with the control group, 11 of the 20 patients had deteriorated over this period yielding a p value of < 0.0008.

A favourable response to oxygen is by definition an indication of hypoxia and should re-direct our attention to evidence of blood vessel involvement in the disease. Typically, there are lesions in the cerebellum of patients with MS. Current immunological ideas would have us believe that these lesions and the accompanying grossly dilated vein are the result of an isolated focus of autoimmune activity in the surrounding tissue. Because of the abundant evidence that oxygen influences the cerebral vasculature in general, and the cerebral veins in particular, it is vital that we re-examine fundamental aspects of this disease.

Multiple sclerosis is, of course, not a diagnosis but a pathological description of the appearance of the brain at post-mortem examination. The suggestion that the disease is simply demyelination of fibres in the white matter may lead to the feeling that the condition is curable, but the loss of cells, fibres and the gliosis in lesions contradicts this. Established multiple sclerosis is simply a reference to multiple scars in the central nervous system and, as such, must represent an incurable condition. The preservation of fibres stressed by Charcot is never more than "relative" and Simpson has recently emphasized the importance of grey matter lesions in MS, indicating that they are required for the diagnosis. An immunological attack on myelin cannot account for this fibre destruction, nor can it account for lesions in the spinal cord, which sometimes produce

central infarction with preservation of some of the surrounding white matter. This pathology must be accommodated by any hypothesis of causation and not discarded because it is inconvenient.

It is most important to recognize that MS is unique in requiring multiple lesions to develop before a "diagnosis" based on more than one lesion can be made. The question must surely be is there a disease that should be called "monosclerosis"? Reference to the pathological literature indicates that single, silent plaques are a comparatively common finding at necropsy and may even be found in the spinal cord.

In view of neuropathological emphasis on the necessity for grey matter lesions to make a pathological "diagnosis" of MS, and the likelihood of such lesions being associated with disability, has the emphasis on white matter plaques been a red-herring? Every study of plaques and disability has shown that they do not correlate, yet despite this, researchers continue to be obsessed with plaques and even attempt to dissociate the "real" disease from the lesions causing the symptoms.[3] Part of this false trail has been to label the disease "demyelinating" and cause generations of researchers to ignore the constant destruction of some fibres in lesions.

BLOOD-BRAIN BARRIER DISTURBANCES

Both radio-isotopes in the 1960s and contrast-enhanced CAT in the 1970s have shown that the blood-brain barrier is disturbed in acute attacks. The extreme sensitivity of nervous tissue to the acute oedema resulting from this dysfunction is well known, and the oligodendrocytes, whose cellular processes form the myelin sheaths, are the cells most vulnerable, not the neurone itself. The damage occurs in the CNS within hours and, whatever the cause of this disease, the initial symptoms must be treated early to prevent permanent damage and disability.

In view of this, the results of the New York hyperbaric oxygen trial, in which severely affected chronic stable or chronic progressive patients with a minimum diagnosed disease duration in excess of five years were chosen, are remarkable.

An agent found to be of benefit in the advanced disease must surely be used at the onset, especially when the agent is a powerful physiologically active substance with known properties. Successful treatment often indicates the pathological mechanism, and the considerable evidence that the *initial* lesions of the disease are caused by fat globule micro-embolism has recently been published.[4] This resulted from a study of decompression sickness affecting the nervous system, where gas bubbles can produce multiple sclerotic plaques in the spinal cord. Fat is the only other material known to reproduce the white matter plaques of multiple sclerosis in man and it is the only agent known to cause an acute and progressive leucoencephalopathy.

Unfortunately, the suggestion that fat embolism is the cause of MS has been interpreted by some as meaning that all the attacks patients suffer are due to embolism. It is only suggested that fat embolism is responsible for the initial damage to blood vessels at the onset of a new symptom.

Evidence of vascular damage has even been found to precede the onset of symptoms by 12 hours,[5] but the existence of blood-brain barrier disturbance is massively documented in acute attacks and has answered the question of which comes first, the vascular disturbance or the demyelination, because the radiolucency develops after a delay of several weeks. It is suggested that this crucial barrier may not heal completely, leaving the area vulnerable to the many onslaughts it is designed to resist. Most subsequent attacks therefore represent a relapse of existing symptoms triggered by anything that stresses the blood-brain barrier, from a common cold to a hot bath.

The evidence of this blood-brain barrier disturbance provided by modern scanning aids simply confirms the careful necropsy studies undertaken by Broman nearly 40 years ago. The integrity of the blood-brain barrier is, of course, a function of the oxygen content of the perfusing blood. Lower the blood oxygen tension and barrier dysfunction leads to diapedesis of red cells and the classical petechial haemorrhages of MS must indicate hypoxia, the cause is irrelevant, the action to be taken is obvious. We surely do not need to validate further the efficacy of oxygen.

Enlisting the aid of the latest and most exciting developments in scanning, NMR imaging has allowed the effect of hyperbaric oxygen to be illustrated in a patient with chronic MS. A scan immediately before and after a 90-minute hyperbaric oxygen session at twice atmospheric pressure has shown vasodilation in a periventricular plaque. A further scan which followed a course of 20 further sessions after a delay of three weeks shows the margins of the lesions are more circumscribed. The treatment was associated with considerable subjective benefit to the patient.

BLADDER FUNCTION

Commenting on these very preliminary results, Schumacher[6] has revealed that neurological expectations in MS are based at an unrealistic level. "To nail down the case for hyperbaric oxygen therapy," we would "have to show a reduction in the number or size of lesions in a controlled study."

Waiting the five years necessary to complete further double-blind trials to offer some amelioration of symptoms in patients with an established incurable disease seems, in view of the evidence, inhumane. Every study has confirmed improvement in bladder function and this has been carefully measured and documented. Bladder problems cause great distress to patients and are such a major cause of morbidity and mortality in the disease that this alone would justify widespread introduction of the therapy. Fortunately, the charity Action for Research into Multiple Sclerosis agrees with all these points and is establishing hyperbaric centres for long-term studies. Already six centres are operating in the UK.

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AN OPEN LETTER TO ALL BAROMEDICAL PHYSICIANS

Richard A Neubauer

I am concerned about the current worldwide explosion in the treatment of multiple sclerosis (MS) with hyperbaric oxygen (HBO). My concern is specifically about certain of the protocols being used for treatment.

At Ocean Medical Centre in Florida, we began our work with HBO for MS in 1973. The first publication of our studies was in 1978.[1] The original data provoked enough interest to lead to the funding of two animal studies.[2,3] A well-documented human trial was later performed by Fischer et al at New York University.[4]

In addition to these controlled research studies, there have been clinical studies involving up to 2,000 patients worldwide, to date. Following the publication of the results from the first 250 MS patients at Ocean Medical Centre,[5] I presented a report on the similarity of results between 500 MS patients and 100 MS patients treated in Italy, at the 5th Congresso Nazionale della Societa Italiana di Medicini Subacquea e Iperbaric in October 1982.[6] At the 8th Annual Conference on Clinical Applications of HBO in Anaheim, California in June 1983, I presented an international survey of reports on the HBO treatment of 1740 MS patients.[7] This was followed in September 1983 by an update and compilation of further controlled and/or longitudinal studies either underway or in the planning stages, presented at the First European Conference on Hyperbaric Medicine.[8] Many other reports have been published.[9,14,17,18]

One overwhelming fact stands out in these studies: All report encouraging results. Yet I receive several telephone calls and letters each week from MS patients regarding the deterioration they are experiencing with HBO. Rarely do I hear from their physicians.

Why is this? Especially in view of the extensive positive published reports. I believe that it is because these patients are being treated at a fixed pressure of 2 ATA (and occasionally higher), usually in a monoplace chamber.

For some reason, the fixed pressure protocol has been adopted at most centres which have started to treat MS with HBO since Fischer's publication. There is no concern about treatment differences between monoplace or multi-station chambers. The differences in the effect on the PaO_2 should be obvious to any baromedical physician (eg. Fischer's PaO_2 levels varied widely even with a fixed 2 ATA protocol in this multistation chamber). In the monoplace chamber, the PaO_2 is directly related to the pressure being used.

There is a scientific basis for the use of a variable, low-pressure protocol. My development of this approach was not entirely empirical. Research by reputable scientists, including Holbach, Wassman et al[14] and Kelly et al[15] clearly indicates that low and variable pressures are preferable in chronic neurological diseases.

This variable, low-pressure protocol has been widely used both in research and in clinical treatment. At Ocean Medical Centre we have treated over 700 MS patients with it. None have deteriorated due to pressure. The work of Fischer, et al[4] also lends support to this protocol. Their results showed that better clinical improvement occurred in patients having PaO_2 levels equalling those in a monoplace chamber at 1.4 - 1.6 ATA. Careful reading of that report would lead any physician to adjust the 2 ATA protocol downward, especially when using a monoplace chamber.

Additionally, the article recently published by Golovkin[16] in the USSR showed that MS patients exposed to pressures over 2 ATA for 20 minutes deteriorated rapidly. He now treats at 1.7 ATA in a multi-station chamber. Similar experience by Pallotta[17] and others in Italy led to the adoption of reduced depths. Davidson and James in Scotland,[11] using a multi-station chamber, changed from the Fischer protocol of fixed pressures to a lower beginning pressure protocol with improved results. Pressure is particularly critical to MS patients with abnormal nervous tissue, especially when optic neuritis is present.

There are three types of MS patients:

1) Newly diagnosed with early symptomology.
2) Stable chronic progressive.
3) Chronic progressive in exacerbation (relapsing/ remitting).

The variable pressure protocol starting at 1.5 ATA and ranging to 2 ATA is well established as effective in stable chronic progressive MS patients (type 2). Most of the published data on MS and HBO deals with type 2 patients. Invariably, HBO treatment leads to encouraging results when appropriate follow-up HBO treatments are given. Long-term longitudinal studies indicate that these patients secure alteration of the course of the disease.

Fewer early cases have been treated with HBO. They invariably respond, as they do with any other modality that is used. Further study is needed in this area. Such patients would have to have a longer follow-up period and more patients would be needed to differentiate between actual alteration of the disease and a placebo effect. James' comparison of decompression illness and MS led to his conclusion that all newly diagnosed MS patients should have HBO with the same priority as in decompression illness. (See his article in "Pressure Points", 13(5): 7-8, 1983 which appears on page 16).