CHAPTER

Hyperbaric Oxygen Therapy in Multiple Sclerosis

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1 INTRODUCTION

Multiple sclerosis (MS) is a disease associated with clinical evidence of disability attributable to more than one lesion in the nervous system. The lesion is classically described as "demyelination with relative preservation of axons." The axon loss in typical lesions in the spinal cord has been shown to be about 20% (Putnam and Alexander 1947). There are between 100 and 150 patients per 100,000 of the population of Western countries, but MRI has demonstrated asymptomatic lesions in up to 40% of the population (James 1997). The disease runs an intermittent course and the initial diagnosis conventionally requires a minimum period of a month between attacks. Single attacks of the same disease process can occur, as in optic neuritis, and may result in permanent disability.

In such patients the disease may remain monosymptomatic, but about three quarters of them when imaged at the time of presentation have other lesions in the brain. There is poor correlation between the patient's disability and the pathology found in the brain at post-mortem, but small lesions in the brainstem and spinal cord are usually associated with clinical signs and symptoms. The clinical course is extremely unpredictable. Patients who satisfy the criteria for multiple sclerosis are described, after several attacks and often with increasing disability, as having "relapsing remitting disease." In a much smaller number the disease may be "chronic progressive" from the onset. Sometimes the patient stabilizes but with disability and is then described as having "chronic static" disease. It is clearly essential that any effective treatment must be started before irreversible glial scarring has developed. There are several reports of the successful treatment of monosymptomatic disorders of the nervous system. such as Bell's palsy (Racic *et al* 1997). using hyperbaric oxygenation. Expterience in treating focal disease in the nervous system has also been gained from divers with blood-brain barrier disturbance in decompression sickness.

2 PATHOGENESIS

It is now accepted that MS is an inflammatory disease of the nervous system (McDonald 1992) in which there is damage to the blood brain barrier, as has been shown in vivo by imaging with enhancement (Aita *et al* 1978, Pozzilli *et al* 1988). The release of plasma proteins into the nervous system tissue is associated with activation of the complement cascade. Although autoimmunity has been a popular etiological concept, all the immune markers investigated in MS have also been found in stroke patients and at the same levels (Wang *et al* 1992). The abrupt onset of symptoms, dissemination in time, the affected sites, and the blood-brain barrier dysfunction all point to a vascular mechanism. There is strong circumstantial evidence that the common cause of the disease is rnicroembolism due to failure of the pulmonary filtration of circulating debris, including fat (James 1982). Neuropathologists have observed that the late lesion of acute fat embolism is indistinguishable from the acute lesions of MS (Scheinker 1943; Courville 1959; Sevitt 1962; Lumsden 1970). The same focal lesion results from microbubble damage to the blood-brain barrier in decompression sickness (Hills and James 1991). However, other mechanisms may also cause focal breakdown of the barrier which is associated with edema, and inflammatory cell invasion. Magnetic resonance spectroscopy has shown a lactate peak in acute new lesions, indicating a failure of oxygen delivery (Miller *et at* 1991).

3 RATIONALE FOR HBO THERAPY

The focal edema that characterizes lesions typical of MS inevitably increases the diffusion distance for oxygen and provides a sound rationale for increasing the oxygen concentration of the plasma under hyperbaric conditions. This increases the gradient for transfer into the tissue. The calibre of the cerebral vasculature is related to the oxygen tension of the perfusing blood and the blood-brain barrier is oxygen dependent. The effectiveness of HBO in the reduction of global cerebral edema has been demonstrated by direct measurement in man (Sukoff & Ragatz 1982) and Rockswold *et al* (1992) have shown that HBO reduces the mortality of severe head injury by 50%. In 1986 Neubauer and Kagan showed the effect of HBO on the edema associated with MS (Figure 20.1). They found that one or more lesions shown on MRI disappeared in 11 of 35 patients (31.4%) after 1 hour of treatment, which suggests that it is the resolution of focal edema that accounts for the improvement.

When natural remission occurs in MS, the critical factor in barrier and tissue repair in the CNS is the availability of tissue oxygen. The driving force to increase the delivery to the tissue is the plasma oxygen tension. A mild disturbance of the barrier may simply increase the water content of the nervous tissue, but more severe failure is associated with the extravasation of plasma constituents, including proteins into the extracellular space and thence to neural tissue. This degree of barrier failure primarily causes damage to myelin. The most severe form of blood-brain barrier failure is associated with perivascular extravasation of red blood cells and tissue necrosis.

Using the animal model *experimental allergic encephalomyelitis* (EAE), Warren *et at* (1978) showed that daily HBO completely suppresses the development of paralytic disease in rodents for at least 34 days. Prockop and Grasso (1978) also found amelioration of EAE in guinea pigs. Hansbrough *et at* (1980) demonstrated that HBO is immunosuppressive in mice. Abbot *et at (1994)* showed that the inflammation produced by the tuberculin reaction in man can be associated with a developing tissue hypoxia that results from edema limiting the rate of oxygen flux at a time when the area is being invaded by highly metabolically active cells.

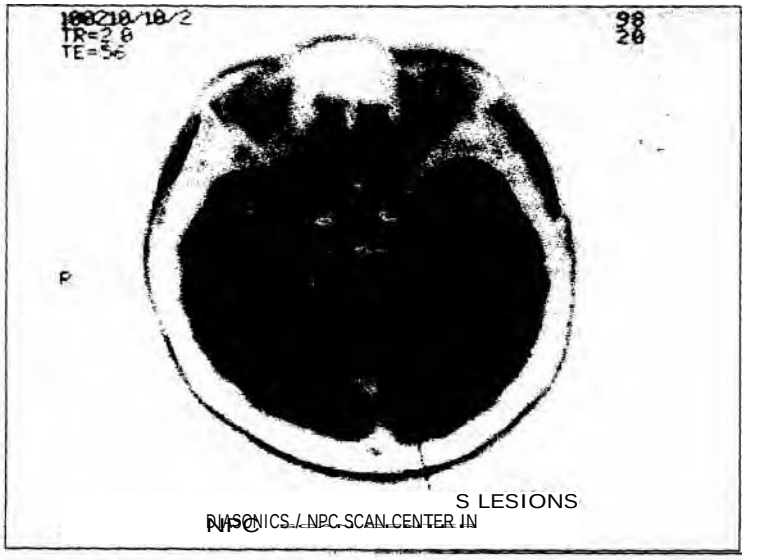

Figure 20.1A

Magnetic resonance image of a patient with multiple sclerosis showing two large lesions in the pons.

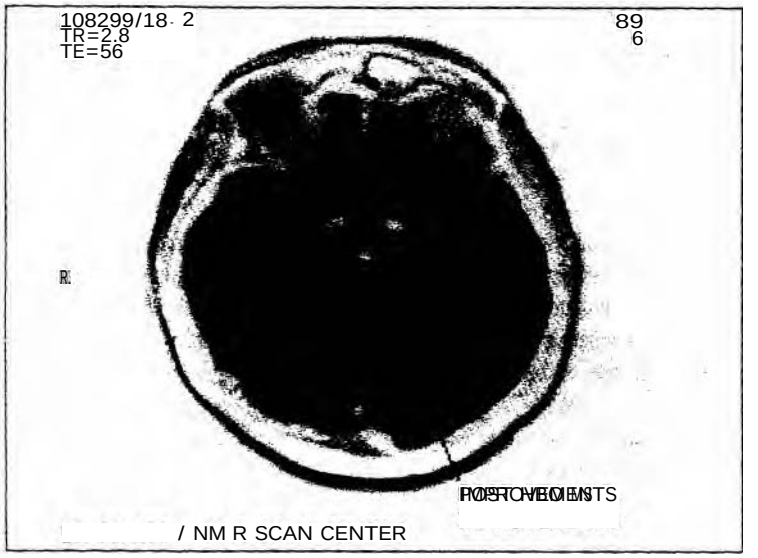

Figure 20.1B

Image after oxygen treatment showing improvement of the MS lesions (Illustrations Courtesy of Dr. Robert Kagan, MRI Scan Center, Fort Lauderdale, Florida).

4 CLINICAL TRIALS OF HBO IN MS

Boschetty and Cernoch (1970) were the first to report the use of HBO in MS patients. In 26 patients they used two 30 mm sessions at 2 ATA daily for 10-20 days. Symptomatic improvement occurred in 15 but was of limited duration. Baixe (1978) compared the symptoms of MS to those of decompression sickness and reported favourable results in 11 patients. Neubauer (1978) independently confirmed the effect when, in 1975, he used HBO for a patient with osteomyelitis who was also suffering from MS. The course of HBO markedly improved the patient's neurological symptoms. Italian reports (Pallotta *et al* 1980: Formai *et al* 1980) also described a beneficial effect and some longer term studies were undertaken.

These uncontrolled studies influenced the design and execution of the first randomized. placebo-controlled, double-blind study by Fischer *et al* (1983). They studied only

patients with a low Kurtzke disability score -KDS (Kurtzke 1961) and matched patients in the experimental and control groups according to age, sex, age at onset of the disease, duration and type of disease, and disability before randomization. It was shown that at 2 ATA once a day for 90 minutes, 5 days a week to a total of 20 treatments, objective improvement in mobility, fatigue, balance and bladder function occurred in 12 of 17 patients ($p < 0.0001$). Those patients having a less severe form of the disease had a more favourable and long lasting response. In contrast, only 1 out of 20 placebo-treated patients showed a positive change. After one year, with no further treatment the treated patients had deteriorated less than the controls ($p < 0.0008$). The authors appreciated the necessity for further studies, particularly in the treatment of acute attacks and the effect of long-term treatment.

This was the first double-blind controlled study and has provided a standard against which other studies should be compared and indeed no other trial has been undertaken in this way. It also set several unfortunate precedents. It used a fixed pressure (2 ATA), limited the number of sessions to 20, and did not employ continuation therapy. The blood-gas measurements indicated that oxygen breathed from a mask gave an effective average alveolar paO2, of 998 mmHg or 1.3 ATA with a range of 1.1 to 1.5 ATA. Most other studies have been undertaken at 2.0 ATA or more with arterial oxygen tensions in the range equal or greater than 1.8. to 1.9 ATA. There is good evidence that the reduction in vessel calibre in the lesions of chronic MS will make patients more sensitive to the vasoconstriction induced by oxygen. Holbach *et al* (1972) have produced evidence that the optimal inspired partial pressure of oxygen in the injured brain of stroke patients is about 1.75 ATA.

Subsequent trials have been of variable quality and have used patients with very long disease duration and often with stable disabilities. They have been extensively reviewed by Gottlieb and Neubauer (1988). Barnes *et al* (1985), after dismissing HBO therapy on the basis of preliminary findings, despite overall significance ($p < 0.01$), called for further studies in their final report (Barnes *et al* 1987). Their follow-up of patients who received HBO showed that the bladder improvement present after one month of treatment ($p < 0.03$) was maintained for 6 months without additional treatment. After a year there was less deterioration in cerebellar function compared to controls ($p < 0.05$). Wiles *et al* (1986), in

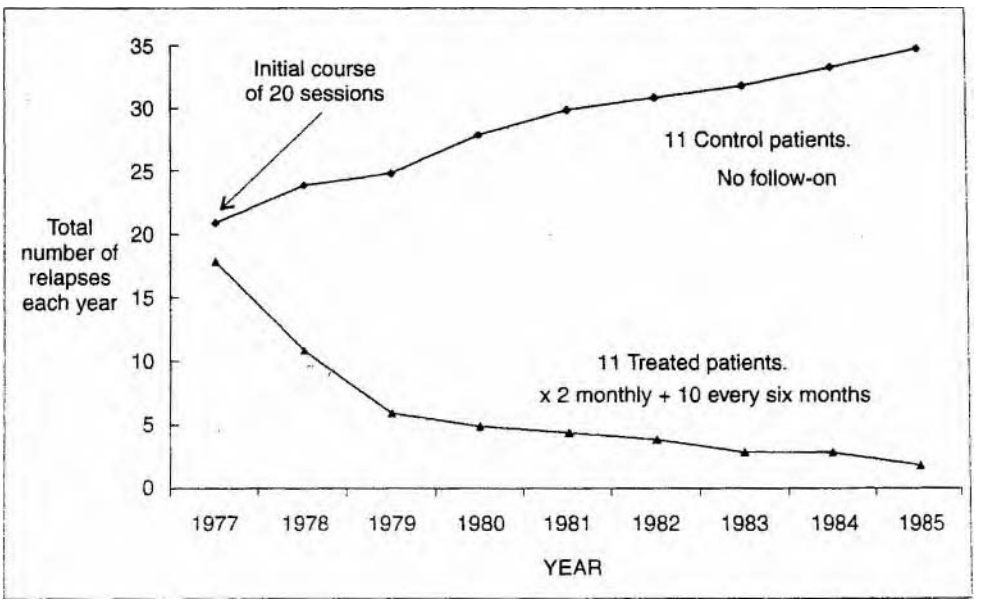

Figure 20.2

Incidence of relapses in 22 patients with and without regular HBO treatment, followed for 8 years. From Pallotta *et al* (1986), with permission.

the second UK study, recorded objective improvement in bladder function in their most severely affected patients under controlled conditions ($p < 0.03$) using cystometry.

Two controlled studies have reported sustained benefit with follow-on treatment. Oriani *et al* (1990) used patients with a low KDS disability score and compared 22 controls with 22 patients treated each week for a year. They detected an appreciable difference in outcome ($p < 0.01$). Pallotta *et al* (1986) followed 22 patients for 8 years. All received an initial course of 20 HBO treatments, and 11 were treated thereafter with 2 exposures every 20 days. The frequency of relapses decreased dramatically in the prolonged treatment group whereas they gradually increased in the group which received only an initial course of treatment (Figure 20.2).

Following these reports, patients established a charity now known as *The Federation of Multiple Sclerosis Treatment Centers,* and they have installed multiplace HBO facilities throughout the United Kingdom (Figure 20.3).

Figure 20.3

The location of the Centers.

The problems associated with the evaluation of any treatment for MS are widely appreciated. Dr. George Schumacher (1974), a former chairman of the International Federation of Multiple Sclerosis Societies, considered that MS does not readily lend itself to double-blind studies because of the unpredictable fluctuation of signs and symptoms. He believed that the best experimental design for investigating the effectiveness of a therapeutic regime is a longitudinal one involving large numbers of patients who serve as their own controls. He suggested that the sole criterion of efficacy should be the arrest of further downhill progression in an overwhelming majority of patients over a two year period, a view now supported by the fact that only long term studies have shown persistent benefits from HBO.

Since 1982 the Federation have treated over 11,000 patients and more than a million individual exposures have been administered without significant incident. They were therefore in a unique position to evaluate the effectiveness of prolonged courses of HBO in a considerable number of patients over 10 or more years.

Seven hundred and three patients were followed in detail since first receiving treatment (Table 20.1).

They breathed oxygen from a face mask in a chamber compressed with air. Five daily treatments of one hour were given at 1.25 ATA. If two or more symptoms improved, a course of twenty treatments in 4 weeks was completed at this pressure. Otherwise the pressure was raised in weekly increments of 0.25 ATA until a response was obtained or five treatments at 2.0 ATA had no effect. Thereafter the patients were invited to return for a "follow-on" treatment on a weekly basis, or failing that, as often as they felt the need or found it possible.

Patients were interviewed and assessed immediately before the initial course when the MS Type and the KDS were determined. A further assessment was made immediately after the initial course of 20 daily treatments. About 70% of patients obtained relief of two or more symptoms (Table 20.2)

The bladder improvements observed in other studies were confirmed (Tables 20.2 and 20.3).

In general, the response was better in patients with less advanced disease. Lower pressures than those used by others were found to be effective, while the initial response was found to be an unreliable guide to the outcome of prolonged treatment.

Further assessments were made between two and four years, and again between six and eight years after the initial course (Perrins and James 1994). They suggested that the initial improvements were being maintained by regular treatment (Table 20.4):

Table 20.1
Patients Recruited to the Study

	FEMALES	MALES	total
	464 = 66%	239 = 34%	703
Mean age (range)	47 (20–70)	47 (19–73)	
Average duration of MS (range)	14 years (0–54)	15 years (0–50)	
Diagnosis confirmed by neurologist	670 = 95%		
MS Type			
Relapsing/Remitting	126 = 18%	41 = 6%	167
Chronic Progressive	262 = 37%	155 = 22%	417
Chronic Static	76 = 11%	43 = 6%	119

Table 20.2
The Patients Assessment of Symptomatic Response to Initial Course

	n	Improved %	No change %	Worse %
Fatigue	567	70	22	8
Speech	187	64	34	1
Balance	562	59	37	4
Bladder	523	68	30	0
Walking	638	77	19	4

Table 20.3
Urinary Frequency of 523 Patients – Before and After Initial Course

	Sum total of times voided Before initial course		After initial course		Improvement
Frequency		$\bar{x}$		$\bar{x}$	
– at night	1232	2.4	651	1.2	47%
– during the day	3873	7.4	2960	5.7	24%

Table 20.4
Specific Abilities Regained after Initial Course and Maintained 2 or 4 Years Later

n = 703	After initial course %	With 0–227 treatments 2 years after initial course %	With 1–104 treatments in 4th year after initial course %
Brushing teeth	39	26	20
Doing up buttons	81	54	40
Threading a needle	50	34	29
Holding a cup	54	46	23
Brushing hair	48	33	26
Fastening brassiere	25	22	11
Cutting up food	36	11	18
Shaving	30	11	18

Abilities	
regained	maintained
67% of 410	73% of 276

A third survey was conducted between ten and fourteen years. By now 126 patients had died (8% were over 60 years old when first treated), 99 had become "lost to follow up," 29 had suffered injuries that affected their Kurtzke value and 2 had had their original diagnosis revised; 447 patients therefore remained for an assessment (Table 20.5). This shows that 103 (23%) were no worse after regular treatment for 10-14 years. Even more remarkable are the 30 patients (7%) who have actually improved.

An analysis reveals that about 300 treatments in 10+ years (about one treatment a fortnight) are required to retard the progression of Relapsing/Remitting patients, while more than 500 treatments (say, once a week) are more effective (Figure 20.4).

Very long-term double-blind controlled studies are not possible as patients do not comply with their allocation. However it is possible to compare groups of patients who have received different treatment regimes (Figure 20.5). The importance of regular treatment is shown at all points examined.

Although there is wide variation in the rate and pattern of decline, the majority of MS patients deteriorate over a two year period of observation (Schumacher 1974). In this study the five Relapsing/Remitting patients who had less than 10 follow-on treatments had deteriorated by 2.0 on the KDS after 10+ years, while the 31 who received more than 400 had only deteriorated by 1.1 (P 0.001). This represents a difference of being able to walk without assistance and the need to use two sticks, or the ability to walk 200 m and being confined to a wheelchair.

The treatment, as administered by the Federation, has been shown to be practicable and cost-effective. After 10 or more years 38 % of the 447 patients were still attending regularly. There were no side effects. The cost of each HBO treatment is about the same as for a haircut, so that relief may be obtained for less than £300 ($ US 450) a year.

Many patients continue to attend as their symptoms, particularly frequency of micturition, are only controlled by regular attendance. Some arrange their holidays so as to be near a Center. Some patients have difficulty in reaching a Center and are so dependant on regular treatment that they have installed monoplace chambers in their own homes.

5 CONCLUSION

The findings of all the long-term studies of established MS patients suggest that regular HBO favorably influences the course of the disease.

This implies that treatment should be instigated as soon as the condition is diagnosed and before irreversible lesions have become established. As might be expected, the response has been shown to be better in patients with less advanced disease and is related to the frequency and continuity of treatment. The social and economic advantages to be gained from regular and prolonged treatment are obvious. There are no side effects.

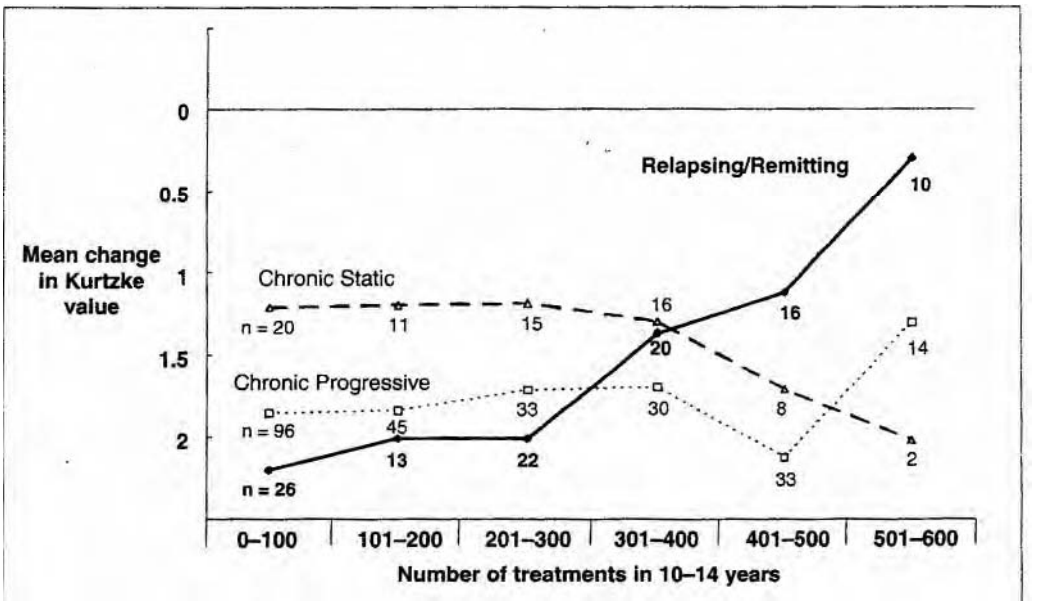

Figure 20.4

The mean change in Kurtzke value related to the number of treatments in 10-14 years.

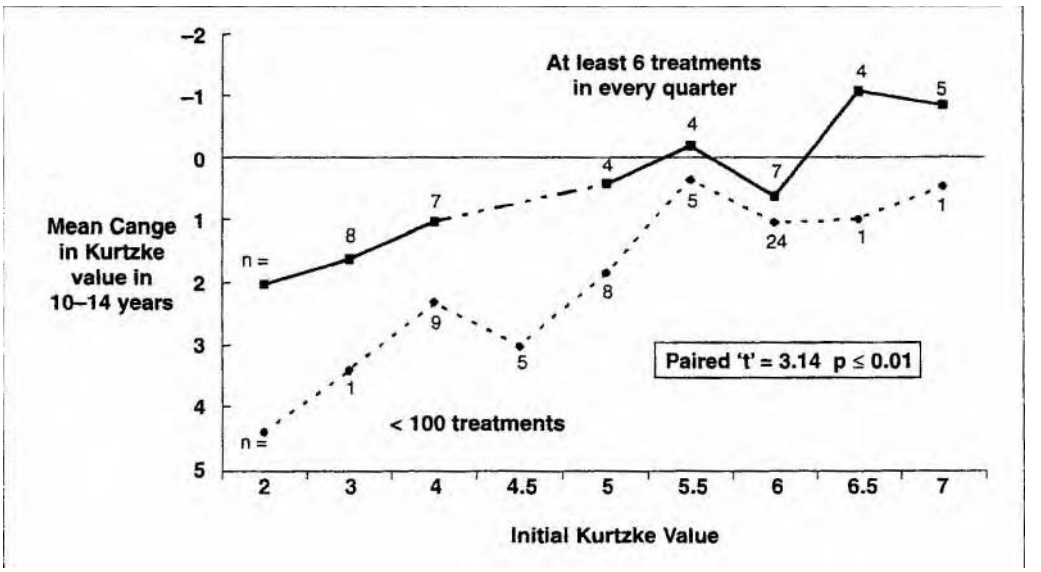

Figure 20.5

Patients, of all types, who received at least 6 treatments in every quarter *versusthose* with less than 100 in 10-14 years.

Table 20.5
Patients Who Were No Worse after Regular Treatment for 10–14 years

447 patients		112 Relapsing / Remitting	259 Chronic progressive	76 Chronic static
Improved	30 = 7%	14 = 13%	12 = 5%	4 = 5%
Unchanged	73 = 16%	23 = 21%	31 = 12%	19 = 25%
No worse	**103 = 23%**	**37 = 33%**	**43 = 17%**	**23 = 30%**
Mean no. of treatments		*338*	*257*	*266*