Hyperbaric Oxygen Therapy for Multiple Sclerosis Patients: where are we now?

The first MS Therapy Centre opened in Dundee in August 1982 and now there are over 100 chambers in operation in 65 therapy centres distributed throughout the UK and the Republic of Ireland. Many wonder why the "establishment" still has difficulty accepting that more oxygen can benefit patients with multiple sclerosis and other neurological diseases. It is particularly surprising in view of the brain's large demand for oxygen, so it is worth reviewing what has happened. The usual comment from doctors is that the controlled trials have shown that oxygen treatment under hyperbaric conditions is of no value in multiple sclerosis patients. This is incorrect, because the trials did show benefit, but not enough to persuade the specialists that it is worthwhile. The key question is whether or not it is sensible to base such a trial on patients with multiple sclerosis 'scarring' – often of ten or more years duration before using more oxygen. It is little wonder that the level of benefit shown was limited.

Hyperbaric Oxygenation: The Controlled Studies

Reports of the value of more oxygen from four countries led to the funding of a double-blind controlled patient trial in 1978 at New York University by the National Multiple Sclerosis Society of America. The Society had already funded two successful studies of hyperbaric oxygenation in the animal model, which has been the basis of research into MS since about 1948. The results of the human study that was undertaken in New York were presented at a meeting in Long Beach California in 1982 by Dr Fischer and clear!y indicated, under the most stringent scientific conditions, that patients with established chronic MS could benefit from more oxygen. The study was published on January 31st 1983 in the New England Journal of Medicine. The expression "more oxygen" emphasizes that the oxygen is the same as in air. We all breathe oxygen under pressure - atmospheric pressure. The role of a pressure chamber in the delivery of oxygen is to allow more oxygen to be dissolved in the water component of the blood, that is, the plasma, in just the same way that carbon dioxide is dissolved in water to create fizzy drinks. Strictly controlled studies of oxygen cannot be undertaken, because oxygen, that is the oxygen in air, cannot be withheld from the control patients as it would be fatal. The studies are then examining an adjustment of oxygen dosage. Fischer and co-workers recommended that further studies should be aimed at patients with acute attacks and to determine long-term benefit, but these have not been undertaken.

Two British studies were set up after the New York Study by Fischer and the results given in preliminary publications appeared to counter the positive results of the New York study. However, neither study had been conducted properly. In the successful New York trial patients had first been matched in pairs and then randomised to either the treated or the control groups. This is essential because of the wide variety of problems patients have, but the Newcastle and the London studies did not match patients. If a patient has been wheelchair bound for ten years there is obviously less chance of improvement than a patient affected for, say, 1 year. The authors of the Newcastle report admitted that the benefit to bladder and bowel function was demonstrated scientifically, but felt that as good an effect could be obtained from drugs. In

their final report, they stated that the improvement in bladder function from the twenty sessions in the chamber had lasted for six months and that the oxygen therapy had reduced the rate of deterioration. The preliminary report in the Lancet in 1985 concluded that hyperbaric oxygenation was of no benefit in the management of MS, but in the final report, in the Journal of Neurology, Neurosurgery and Psychiatry two years later, they called for more studies to be done. The Lancet paper had been given great publicity by a release to Associated Press from the MS Societies in 1985, but the final report went without comment. The London trial published in the British Medical Journal also found positive results in bladder function, but these were the only results given as the rest of the findings were expressed as a statistical table which is unique in this type of journal. Trials in other countries, for example Canada, deliberately chose stable patients with very long-term disease, which is nonsensical when the aim of giving the additional oxygen is to improve the level of remission.

The papers from the Glasgow ARMS centre and the painstaking follow-up of results from over fifteen years' experience in the ARMS centres by Dr Perrins have shown beyond doubt that regular hyperbaric oxygenation can benefit the majority of patients by stabilising their condition, although it cannot, of course stop the effects of ageing. Despite the call for long-term studies the publication of this study has been consistently resisted by journal referees.

Oxygen: an Orphan Drug

Why is there such resistance to giving more oxygen under hyperbaric conditions, not only in MS, but also in a wide variety of diseases where it could save lives and improve the outcome of treatment? The principle reason is that it is not marketed, because it cannot make money. Linked to this, it is not taught in Medical Schools in the UK, because the current generation of teachers do not themselves understand the importance of barometric pressure in oxygen delivery. If such fundamental concepts as pressure and tissue oxygenation are not grasped properly before a doctor qualifies, then it is almost impossible for them to be taught later. Oxygen is piped to the bedside in most hospitals and it is a major professional confrontation to tell doctors that they are not using it properly. How many physicians can give the correct answer to the simple question why do veins appear blue? Most would reply, it is because blood is deoxygenated. This is wrong. It only requires a moment's thought to realize that if blood is withdrawn from a vein it is dark red, not blue. The origin of the error is simple. When medical textbooks illustrate the circulation, veins are outlined in blue and arteries in red. In general medical students are taught little about oxygen and certainly remember that it can be toxic in excess. Oxygen is toxic when given in excessive amounts for too long, but this is only relevant to divers. We know more about the actions of oxygen and the safe limits than we do about any drug. Millions of man hours of hyperbaric oxygen therapy have been safely administered over the last forty years and the MS Therapy centres in the UK themselves have accumulated over 1.5 million sessions without a significant incident. Over this period there will have been thousands of deaths from over the counter drugs such as aspirin.

Oxygen has been extensively used in military and commercial diving for over sixty years and again millions of hours of oxygen breathing have been completed underwater since the midget submarine charioteers bravely attacked ships in the Second World War. Similarly pure oxygen breathing is necessary in military aircraft and for 'extra vehicular activity' in the space programme. Although these activities have involved thousands of scientists and engineers, very few doctors have been involved and so it is not surprising that most neurologists know very little about hyperbaric conditions and the need for the higher dosages of oxygen possible at increased atmospheric pressure.

It is often alleged that oxygen levels are measured routinely in clinical practice. This is not true. What is measured is the oxygenation of haemoglobin. This value gives no indication of the amount of oxygen reaching the tissues. So in major conditions, as with heart attacks or strokes, the amount of oxygen being carried by the blood may be normal but the tissues of the heart or brain are dying of hypoxia - lack of oxygen. Now a controlled trial in California has shown that when the latest clot busting drugs are given together with hyperbaric oxygenation the benefit is dramatic. (Am J Cardiol September 1998)

MS and Magnetic Resonance Imaging

New insights have been gained into MS over the last decade. Do they mean that we have been wrong to use more oxygen? No, quite the reverse, technology has brought magnetic resonance techniques (MRI) into common use. The MRI scanner donated by the MS Society to the National Hospital for Neurological Disease has been in the forefront of developments and many papers have been published on the appearance of the brain when the first symptoms develop. The problem, ignored over the years, is that multiple sclerosis is NOT a diagnosis, it is a description of more than one scar in the nervous system. However it has been decided by a committee that the "diagnosis" cannot be made until the patient has had two attacks and there is clinical evidence of disability. MS is the only disease to which this 'multiple' rule is applied. It has also been decided that the time interval between attacks must be a minimum of one month. Shorter than this and the patient may be given another "diagnosis." However a first attack can be so severe that the disability can be permanent. Take, for example, severe optic neuritis where the patient has complete blindness, that is, not even the perception of light. Sight may never return, but what disease does the patient have? Is it multiple? The obvious answer is no and therefore a second attack must be awaited for the "diagnosis". It has been documented in one patient that the interval between attacks was 56 years but, of course, a second attack may NEVER take place. If, however, another attack does occur then, by the neurologist's definition, a "diagnosis" of MS can be made and the patient can then be included in trials of treatment. Is it likely that treatment can influence blindness present in an eye after 56 years? The answer is unfortunately all too clear - "no!"

The use of MRI has made matters difficult for those who advocate the traditional approach to MS which requires evidence of two lesions. At the National Hospital for Nervous Diseases in London they have scanned patients with just acute optic neuritis (eye nerve inflammation) causing blurring of vision and pain in the eye and who have no other symptoms or signs. They found that almost all of the patients have multiple areas affected. In other words, in the majority of patients, the start of the multiple areas of sclerosis occurs at a single point in time. However MRI has also demonstrated multiple areas affected in about 10 - 40% of the "normal" population (that is people volunteering as normal controls in a study) between the ages 20 and 50. So, why do they not have symptoms? It is simply because, as is already well-known, large areas of the brain can be damaged and the patient can appear normal and indeed function normally. What matters is not necessarily how much of the nervous system is damaged, but the type of damage and especially where it is. A tiny volume of tissue damaged in the brain stem or the spinal cord will almost certainly give rise to symptoms. Patients with "MS" therefore represent the tip of a very large iceberg of "minor brain damage in the population. The lesions typical of MS are found in all patients of advanced years, that is over 80 years of age, and may also result from an injury at birth.

MS and the Myelin Sheath

One myth perpetuated in MS is that it is simply the myelin sheath that is damaged and if a way of repairing the sheaths or regenerating the cells responsible for them could be found then we could restore

MS patients to perfect health. This is not true and this is evident from the use of the word "sclerosis". When the myelin is damaged in a small area as is typical of MS the nerve fibres are also damaged and in the spinal cord there is a loss of a minimum of 25% of the fibres. Pathologists have emphasized this for a long time, calling it "relative preservation" of the nerve fibres in the areas of damage, but this has been ignored by physicians. What else has MR imaging shown? There is now a method which demonstrates leakage from blood vessels by injecting what is termed a contrast material before the scan is taken. The blood vessels of the nervous system are quite different from any other vessels in the body and are engineered to prevent leakage, because of the extreme sensitivity of the tissues of the brain and spinal cord. The blood contains many substances which can injure these tissues. In an acute attack typical of those that lead to a "diagnosis" such as optic neuritis that start the process eventually leading to scarring, there is leakage from the blood vessels that can be shown on MR imaging. There is nothing new in finding that the blood vessels are the start of the problem, because the very first detailed account of MS by the Swiss pathologist Rindfleisch working in Zurich published in 1863 gave an account of this finding. What does it mean? Inescapably, that we must use a therapy successful in stopping this leakage right at the start of the disease, at the first symptom and this is also obvious from the tact that a patient may never recover from the attack.

However we are faced with a very large number of patients who already have multiple areas affected, so what relevance is all of this to them? Well, the three basic categories of MS are relapsing/remitting, chronic stable and chronic progressive disease. MR imaging has shown that the blood vessel problem is occurring very regularly in relapsing/remitting patients and even in some patients who are regarded by the specialists as stable, but is not generally detectable in chronic progressive patients. What does this mean?

The objective for any therapy introduced in the established disease is to stabilize the patient or, in other words, to induce the best possible remission. The disease process must be limited before scarring takes place. What is the most crucial substance to the induction of remission or healing? - OXYGEN. If we could prove that theire was a deficiency of oxygen in patients with MS or a component of the disease that could benefit from more, then we would have a unequivocal case for giving extra oxygen. More, that is, than is in the air we all have to breathe. Magnetic resonance techniques provided just this evidence using spectroscopy which can detect the chemicals present in a small volume of tissue in the brain ten years ago. At the National Hospital in London they have detected the presence of lactate in the brain of a patient during an acute attack. They have stated in a letter to the Lancet *"both oedema (tissue swelling) and vasculitis (inflammation of blood vessels) have been described in new plaques and it is conceivable that such changes may affect oxygen delivery to cells and so explain the lactate peak that we and others have found."* "Conceivable" is a strange word to use because lactate can only be present when there is lack of oxygen. Doctors have a duty to correct oxygen deficiency but the authors of the Lancet letter did not even discuss giving more oxygen to their patient.

MS and Beta-Interferon

It is interesting that the ground rules for MS trials were changed for the development of beta-interferon treatment. The stated aim is not to improve disability in chronic MS patients, but to reduce the number of attacks. Trials have shown that beta-interferon can reduce the number of attacks over two years in a

group of patients from three to two (on average) but no affect on disability has been found. Unfortunately it actually induces attacks in some patients and may be associated with the development of suicidal depression.

The suitability of the therapy can only be determined by the reaction of the patient. The cost of the drug? The figure quoted is £180 per injection, which is given every other day. Needless to say there should be proper evidence of a long term effect on disability before the NHS pays for this drug. How does the drug work? A new paper indicates that it is by reducing the permeability of the blood-brain barrier and it is a continuation therapy which indicates the importance of the blood-brain barrier. However, an acute relapse can be caused by nothing more sinister than a hot bath which beta interferon is unlikely to prevent. It had been postulated that beta-interferon has an immunological effect but the idea that MS is an autoimmune disease has now finally been laid to rest, although judged by research fund allocations it would seem that the information has had no effect. Researchers in Sweden looked at the immune changes that follow stroke, which is certainly due to a blood vessel problem. Exactly the same immunological changes and in the same quantity were found in *stroke patients* as are found in patients with MS. So the immune changes are not the cause of the problem, they result from it and are actually evidence of repair. Inevitably the interferons have side effects and there are no long-term studies of their safety. A report recently indicates that patients are developing antibodies to the interferon. This may mean that natural immunity, which is necessary to fight infection, is lost.

Where does this leave us as patients or potential patients? There are over sixty MS Therapy Centres and they are doing wonderful work, not only in providing oxygen therapy, but also in the day to day support of MS sufferers. Hyperbaric oxygen therapy has been shown to be simple to use and able to induce a better remission in many patients. Used regularly *it can reduce the rate of progression* and in the charity setting it is inexpensive. One hour of therapy in the USA typically costs about $100-200 because it is doctor controlled, although the oxygen only costs about $2. Hyperbaric oxygen therapy for MS patients must remain outside of the NHS because this guarantees free access for patients. The last thing apatient should have to face feeling the need for more oxygen is to have to justify this to a “specialist,” who would require objective evidence of worsening. Within the Health Service the costs would rise in a major way. In 1987 an article about, The “Inappropriate use of High Technology” in the BMJ singled out as an example the use of hyperbaric oxygen for multiple sclerosis patients. With simple centres run by patients, their relatives and volunteers this has been shown to be an inappropriate comment. Dr David Perrins has been able to follow over 800 patients who have had hyperbaric oxygenation for over 15 years which has shown the stabilizing influence of regular therapy. We in the MS National Therapy Centres must make more MS patients and their family doctors aware of the activities of the centres and the great benefits from the support available to them. If an organization does not grow it dies.

What is the final message ... it is simply ... breathing is important ... it makes you better and if you breathe more oxygen when you are ill and you will get better faster. It is improving on nature.

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