Oxygen, Genes, Inflammation and the Treatment of Multiple Sclerosis

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A new centre will soon begin operating on the Isle of Mull, twenty three years after the first MS Therapy Centre began operations in an industrial unit in Peddie Street Dundee and it is time to take stock. The number of hyperbaric treatment sessions completed in MS National Therapy Centres will soon reach two million and we have full recognition of our centres by the Department of Health for the treatment of neurological conditions in the community, for example, for those with multiple sclerosis and cerebral pa1sy. Note that the term cerebral palsy is not exclusive to children; adults with a stroke have cerebral palsy. In England and Wales, but thankfully not in Scotland or Ireland, the centres come under the Private and Voluntary Healthcare Regulations. Note that hyperbaric treatment is recognized for use in the NHS by the Department of Health, under Specialist Services Definition Set No. 28, but most doctors are not aware of this and this will continue until hyperbaric medicine is taught in our medical schools.

Remember, the only way to access hyperbaric treatment is to ask for it. Although, of course, oxygen is widely prescribed, it is only at a low dosage and as a supplement, not as a treatment. It is understandable that doctors find it hard to accept that breathing a high level of oxygen for just one hour a week in a hyperbaric chamber can improve the course of a serious disease like multiple sclerosis, but this is set to change, not least because the concept of regular treatment is now firmly established for drugs. For example, the object of prescribing the beta interferons, which are injected either every other day, or once a week, is to reduce the rate of progression and note this is for life at £10,000 per year. Attitudes to oxygen in medicine are set to change because of the latest research which is at the cutting edge of science.

Oxygen in Control

Everyone knows that oxygen is needed to obtain energy from glucose, but the latest research has now shown that oxygen is also involved indirectly regulating our genes.[1] It controls the level of a family of proteins, known by the strange name *Hypoxia-inducible Factor* proteins, (HIF) which, translated, stands for *Lack of Oxygen Inducible Factor*. It is a paradox that the level of these proteins *rises* as oxygen levels *fall*. When oxygen levels are normal these HIF proteins, which are produced by every cell in the body, are actually destroyed by another protein, but the rate of this destruction is reduced as oxygen levels fall. The HIP proteins regulate the expression of many genes and over 36 have already been identified, including 12 involved in glucose metabolism. Others control the growth of new blood vessels. If the oxygen supply to a tissue reduces, the genes activate a factor to grow new capillaries. Oxygen is therefore the only agent which can act to correct a deficiency in its own level.

Oxygen also controls the behaviour of white blood cells in inflammation and this means that giving more oxygen is an anti inflammatory treatment. This astonishing information has been published in the most eminent scientific journals, but has not been publicized; oxygen is simply not of sufficient interest to warrant headlines and, as it cannot be patented, it will never be promoted. The research provides indisputable support for using high levels of oxygen as a continuing treatment for multiple sclerosis patients and is an immense endorsement of the tireless work of everyone involved in the MS Therapy Centres in the UK and Ireland over the last 23 years. To highlight the importance of these findings to patients with nervous system problems, especially those with multiple sclerosis, it must be put in context.

It has been known for some time that oxygen is involved in controlling blood flow because the effects on the diameter of blood vessels can actually be seen by looking into the eye. When more oxygen is breathed, the diameter of most blood vessels reduces and, conversely, when less oxygen is breathed, for example, by going to altitude, blood vessels enlarge, which increases blood flow. How oxygen achieves this has, until recently, remained a mystery but it is now known that oxygen controls the size of b1ood vesse1s by acting in concert with another gas, nitric oxide (NO) actually produced in the lining of blood vessels. Nitric oxide acts to increase blood vessel diameter by relaxing the muscle in the wall, but when oxygen levels are high, NO binds to oxyhaemoglobin thus neutralizing its effect. [2] Haemoglobin is, of course, the protein iron pigment which by binding oxygen is responsible for the redness of blood. Everyone knows that the brain and to a lesser extent the spinal cord require a large blood supply to meet their demand for oxygen, but many do not know that they contain some areas where the blood supply is relatively poor and these are the areas where the damage typical of multiple sclerosis is found.[3]

It comes as a surprise to many people that *blood itself* is toxic and must be kept within blood vessels, especially in the nervous system, so that the sensitive cells can be protected from many substances easily tolerated by other organs of the body. Five methods of brain imaging have confirmed beyond question that the disease causing *multiple sclerosis* or indeed *single* areas of sclerosis, *mono sclerosis* [4](both MS) is the result of internal damage to blood vessels [5] which means that the barrier protecting the brain, known as the *blood-brain barrier* fails.[6] The leakage caused precedes the development of symptoms [7] and the effects can often be seen in the eye, as they may also affect the blood vessels of the retina where there is no myelin. [8] As there is an excellent blood supply to the retina and no myelin is present, little damage is caused.

Blood vessels, Inflammation and Current Theories in Multiple Sclerosis

The blood vessel changes in MS were first described by Rindfleisch in Zurich over a hundred and forty years ago [9] but, despite this, they are rarely mentioned in current textbooks and it is still fashionable to invoke a form of self destruction - *auto immunity* - to account for the disease. It is often suggested that this is in some way linked to a virus, but this has never actually been explained. Despite this and the billions spent on the research, much of it supported by the drug companies, there is actually no evidence that the activity of the immune system is actually causing harm. Studies of stroke patients have shown that they have just the same immune changes, even at the same levels, as MS patients. [10] As stroke patients tend to improve, this indicates that the immune changes are *actually involved in recovery, that is repairing the damage*; clearly a very necessary activity. The theory of auto immunity came from research into allergy before the Second World War and allergy involves inflammation. Inflammation is usually associated with infection, but MS is certainly not infectious and no virus has ever been found, despite some patients even being subjected to brain biopsy during attacks. However, in view of the proven loss of the protection afforded by the blood-brain barrier in the damaged areas of MS, it should be expected that blood-borne viruses will cause attacks in patients with established disease. Every MS patient should be told that relapses can be provoked simply by an excessively hot bath, because heat enlarges blood vessels, including those in the brain, causing blood leakage. [11] If this leakage goes unchecked then eventually scars, which are the lowest common denominator of healing in any tissue, begin to develop. As scars represent healing, looking for a cure in MS is looking for a cure for healing.

The Barrier Protecting the Brain -

It may come as a surprise to many to learn that blood - so necessary for life - is toxic. The substances carried in our blood are changing all the time. For example, after a meal the amount of carbohydrate, protein and fat rises. The brain needs to have stable conditions to work properly and the contents of the fluid which surrounds the brain are very tightly controlled. The blood-brain barrier regulates the passage of substances into the brain, so we can think clearly all the time, although it is common to feel sleepy after a large meal! When leakage from damaged blood vessels occurs in an area of the brain or spinal cord containing myelinated nerve fibres there may be damage, either to individual sheaths, or to the parent cell which forms the sheaths, the oligodendrocyte. Note that myelin sheaths do not insulate nerve fibres; they increase the speed at which they transmit nerve impulses - often several hundred times. A single oligodendrocyte may form over 30 myelin segments and so loss of these cells results in significant loss of myelin. In a typical area in MS there is only relative preservation of the nerve fibres and in the spinal cord about 20% of the fibres may be lost in affected areas.[12] Neurons may also be destroyed and it these two factors, rather than the loss of myelin, that are responsible for disability.

Magnetic Resonance Imaging- (M.R.I.) has shown that silent areas characteristic of those found in patients with multiple sclerosis are very common affecting at least 1 in 4 apparently normal people [13] and this is just a *snapshot* in time. It is likely that we all have small areas of damage from time to time, but without any symptoms and these areas heal naturally without any treatment, as long as there is sufficient oxygen available to the tissues. This natural healing has been shown in patients already labelled as MS who have been followed by M.R.I. over a six month period. The researchers injected a dye which transfers into the brain when the blood-brain barrier leaks. It was shown that new areas may form when other areas disappear. It therefore makes sense to help this healing naturally - by giving more oxygen on a regular basis and this is the reasoning behind the use of the interferons, which try to mimic the natural interferons produced by the body. It is likely that those people who develop symptoms have damage in certain critical areas where recovery is restricted by a poor blood supply. Recovery from nervous system damage, that is remission in MS, is now known to include new capillary formation and also stem cells from the bone marrow, which can form new nerves cells: bone marrow can make brain. [14] Fibres and myelin sheaths may also regrow but, of course, all of this requires oxygen.

Multiple Sclerosis, Inflammation and Oxygen

Although most attention has been given to the scarring process, it is universally accepted that the hallmark of MS is *inflammation* and it is associated with the activation of white blood cells with disruption of the blood-brain barrier. 'The behaviour of white blood cells has been a target for drugs designed to stop them sticking and migrating into the tissues. Unfortunately this approach has proved to be a poisoned chalice. *Tysabri*, produced by *Biogen*, which reduces white blood cell stickiness has just been withdrawn. [15] The drug had been fast tracked by the FDA and allowed to be marketed after one year instead of two, but now two patients have, predictably, developed fulminating infections of the brain. Ironically, oxygen actually controls white blood cell stickiness, again confirming the importance of hyperbaric oxygen treatment. Human studies have shown that inflammation may result in a profound lack of oxygen **16** because of the invasion of tissue by white blood cells when the water content of the tissue is increasing; simply, it is becoming swollen. The latest research has shown that as oxygen levels fall, the HIP proteins control inflammation by activating the genes which increase the permeability of blood vessels, white blood cell stickiness and their migration into the tissues, This is the normal response of the body to infection, but,

unfortunately, is inappropriately activated when there is lack of oxygen from any cause even an ascent to altitude! It is reasonable to question if lack of oxygen, that is hypoxia, has been found in MS patients. It has; a development of M.R.I. Magnetic Resonance Spectroscopy, has detected presence of lactic acid in acutely inflamed areas in MS patients. [17] Lactic acid, which is responsible fur the burning sensation in muscles on exercise, indicates lack of oxygen.

Hyperbaric Medicine: Oxygen as a Treatment

Lack of oxygen in a tissue can only be corrected by delivering more oxygen to the affected tissue. Unfortunately we cannot get more oxygen by breathing faster and so we need to breathe a higher concentration and this may need an increase in pressure; that is *hyperbaric* conditions. It is possible, however, that if pure (100%) oxygen was given as an emergency treatment for acute attacks it may be a successful treatment at normal atmospheric pressure. This given urgently, may prevent the tissue destruction which eventually leads to scar formation. In patients with established sclerosis, serial studies over several months using M.R.I. have shown that the blood vessel damage may become chronic and regular oxygen treatment by limiting inflammation may reduce the progression of the disease. The evidence from the MS National Therapy Centres, which have now been operating in the UK for 23 years, [18] based on Class 1 evidence from an excellent controlled trial [19] fully supports this contention. Those doctors who say there is no scientific evidence supporting the use of oxygen treatment for patients with multiple sclerosis need to be told the facts and just how important hyperbaric oxygen treatment is to the continued well being of multiple sclerosis treatment. Most of all we need to make every MS patient aware of our superb centres - we need the oxygen of publicity!

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