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Multiple Sclerosis:

Its Etiology, Pathogenesis, and Therapeutics With Emphasis on the Controversial Use of HBO

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Gottlieb SF, Neubauer RA. Multiple sclerosis: its etiology, pathogenesis, and therapeutics with emphasis on the controversial use of HBO. J Hyper Med 1988; 3(3):143-164-A review of the current hypotheses in the etiology and pathogenesis of multiple sclerosis (MS) is presented together with the implications for therapy. A new hypothesis as to etiology is presented. Special emphasis is placed on the controversy surrounding the use of hyperbaric oxygen in a critical analysis of the published double-blind studies and related discussions. Emphasis placed on the predominant infective and autoimmune hypotheses cannot be supported, either from the pathology of the disease or by the response to treatment. It is concluded that the evidence of beneficial effects of hyperbaric oxygen therapy, despite the use of patients with advanced disease in trials, is very impressive, especially in chronic progressive disease. It is also concluded that there is need for further research and that such studies should examine the effects of hyperbaric oxygenation alone, and in combination with other therapeutic agents, in individual patients with the methods of real-time investigation now available. Meanwhile, based on comparative efficacy and safety, hyperbaric oxygenation is recommended for treating early stages of MS, especially for treating cerebellar and bowel-bladder disorders.

ACTH-cortisone, antiviral agents, copolymer I, double-blind studies, hyperbaric oxygen therapy, immunosuppressants, Kurtzke disability scores, MS etiology, MS pathophysiology, MS therapy, multiple sclerosis (MS), plasmapheresis

introduction

Multiple sclerosis (MS) is classified as a demyelinating disease of the central nervous system (1) and is the most common of the demyelinating diseases. Despite over a century of investigation, MS remains one of the most frustrating diseases for patients and physicians because there is no agreed upon etiology and there is no cure or agreed upon therapy. Perhaps no other disease has had so many therapies proposed and had them fail (2, 3).

The purpose of this article is to review some of the evidence for the etiology and pathophysiology of MS and match the information with current therapies. Specific attention will be directed at a critique of the basis for hyperbaric oxygen (HBO) as a new therapeutic modality for MS (summarized in Table 1). We concentrate on HBO because this therapeutic modality has generated

an extremely emotional, as well as an intellectual controversy, perhaps more so than any previously proposed treatment.

Nature of the Lesion

Irrespective of some details as to mechanism and significance of aspects of the MS lesion, there seems to be a consensus as to the sequence of events occurring in that lesion: the initial event-about which very little is known because of the difficulty of obtaining tissues in the very early stages of the disease-appears to be a blood-brain barrier disturbance, inflammation followed by edema formation and lymphocytic infiltration, vacuolization, and periaxial demyelination, usually with preservation of the axis cylinder, although axonal damage may occur, followed, over a period of months or years, by gliosis and sclerosis; occasionally slight remyelination may be observed in some areas (2, 4, 5).

Virtually nothing is known about the mechanism of the demyelination, and there is controversy concerning the role of the lymphocytes and macrophages: Do they lead to the degradation of the myelin? or, Do they function in clearing the debris resulting from the demyelination? From its initiation, the location in which the series of events occur that culminate in damaged tissue and a scar is referred to as a plaque. In MS there are many such plaques in the CNS in varying stages of evolution, from immature active plaques to mature, inactive plaques (5). The focal lesions vary from 1.0 mm to several centimeters. In contrast to acute lesions demonstrating phagocytic microglia and perivascular infiltration by lymphocytes and mononuclear cells, Chronic lesions are relatively acellular. The plaques seem to be scattered throughout the white matter of the cerebrum, cerebellum, spinal cord, and optic nerves; they may also be found in cortical and deep gray matter. Histologic examination of myelinated fibers in the gray matter also shows demyelination. There does not appear to be any obvious pattern to the location of the plaques, except in the area around the occipital horns of the lateral ventricles where there may be a symmetrical distribution (6). The main sites affected are known to be located in the watershed territories of the CNS. Irrespective of which etiology of MS and which of the mechanisms proposed for the demyelination one subscribes to, one observation about which there is almost universal agreement is that the periaxial demyelination is responsible for the clinical symptomatology.

In addition to the loss of myelin in the CNS, there is meningeal inflammation (7), peripheral nerve involvement (8), retinal changes (9), neuronal loss (10), skin petechiae (11), and vascular changes outside the region of plaque formation (12).

Late in the disease there is often, anatomically, a generalized cerebral atrophy (10, 13) with enlargement of the cerebral ventricles, sylvian and intrahemispheric fissures, and ambient cistern or sulci. Physiologically, one finds, along with impaired motor and sensory functioning, a generalized

cerebral hypofunctioning and a decrement in cognition (13). Brooks et al. (13) reported that cerebral oxygen utilization and blood flow were significantly reduced in white matter and the peripheral cortical gray matter in MS patients as compared to normal controls. The lowest levels of oxygen utilization were found in patients with cerebral atrophy: also, patients with the greatest deterioration in IQ had the lowest levels of oxygen utilization. These investigators found no region of cortical hypofunction or atrophy that corresponded with specific regions of cortical impairment as revealed by psychometric testing. Although Brooks et al. (13) claim they found no ischemic tissue with raised oxygen extractions, technical limitations may have masked such findings; their CT equipment had a resolution of 1.7 cm, whereas focal plaques may be 1 to 2 mm in length. This technical limitation also may explain why they did not find plaques in the cerebellum.

Significant observations include the geographic relationship of plaques to veins, edema formation, and the apparent cellular, astrocytic, response to the edema. Physiologically, edema elevates local tissue hydrostatic pressure, which restricts blood flow and thereby interferes with oxygen and nutrient delivery and diffusion and elimination of metabolic wastes. Focal ischemia and edema result in a localized hypoxia, thereby decreasing the energy metabolism of affected tissues. The foregoing conclusion is greatly strengthened by the findings of Kelly et al. (14) who measured oxygen tensions in injured nervous tissue. They demonstrated a decline in tissue oxygen tension following a standard injury, the failure of normobaric oxygen to alleviate the hypoxia, and the marked increase in tissue oxygen tensions following HBO exposure, with appropriate clinical improvement associated with the increased availability of oxygen.

When viewed from the perspective of what is known and being learned about the role of oxygen in wound healing, an interesting new concept begins to emerge which has marked significance for guiding new research and therapeutic directions with respect to demyelinating diseases in general and MS specifically, i.e., MS should be viewed as a wound in the CNS and approaches to therapy should incorporate knowledge that has been gained from the field of wound healing.

Etiology

Despite the existence of different hypotheses as to the causation of MS, there is a marked dearth of substantive information concerning its etiology. The two most prominent hypotheses center around the infectious and autoallergic models (2, 15-17). These two hypotheses, independently or in their combined form, have exerted a powerful influence over the field for the past several decades, despite the absence of supporting data or the presence of data to the contrary.

Viral

There is no direct evidence that a virus initiates the disease process(es) associated with MS, nor is there evidence that a virus is a persistent component of the unfolding course of the disease. To date, all efforts to isolate a virus from the CNS of MS patients that meets Koch's postulates have been unsuccessful (15, 17).

This does not imply that a viral etiology of MS may not eventually be confirmed. There are many problems associated with isolating latent viruses. However, popular current trends must not hinder the growth and exploration of competing hypotheses.

Immunologic

A body of evidence exists indicating abnormalities in immunologic control mechanisms in patients with MS: whether these are a cause or a result of the disease is unknown (2, 5, 15, 18). The autoimmune etiology of MS implies specificity of the demyelination; yet, the involvement of the peripheral nervous system indicates a relative nonspecificity of the etiologic agent (19).

From the supposed similarities of the pathology of experimental allergic encephalopathy (EAE) to that of MS, EAE has been championed as an appropriate animal model (2, 16, 20) although its suitability has been questioned (5, 18, 21). MS and EAE differ from one another in one very important respect: in MS, perivascular infiltration and cellular inflammatory response follow myelin destruction, whereas in EAE infiltration and inflammation precede the myelin destruction. These differences in demyelination tend to eliminate sensitized cells as the underlying etiology of MS. Yet Hickey and Kimura (22) demonstrated that perivascular microglial cells in rats are bone-marrow derived and can function as endogenous antigen-presenting cells and may function as such in the induction of EAE in vivo, thus suggesting that these cells, unlike endothelial or astrocytic cells, express antigens before the inflammatory response: The other two cell types express antigens either after the inflammatory response in EAE or MS is fully developed or resolving.

Toxic and Environmental

Disenchantment with the viral and immunologic etiologies of MS have strengthened the view that a toxic or environmental factor may be a causative agent of the disease (19).

Recent findings of Spencer et al. (23), demonstrating a linkage of a plant neurotoxin to the high incidence of amyotrophic lateral sclerosis, Parkinsonism, and Alzheimer-type dementia among the Chamorro population in the western Pacific, provided strong evidence of an environmental etiology of these diseases. These findings seem to have put to rest the role of virus and heredity factors in the causation of these and other neurologic diseases (24). Ideas concerning the causation of MS may be similarly affected because one

of the strongest arguments favoring a viral etiology of MS is demographic (25), even though this view has been soundly discredited (18, 21).

Indications of an environmental factor in the causation of certain neurologic diseases lend support to Wolfgram's (19) thinking about the role of a circulating toxin and to James' (26) ideas on the role of subacute fat emboli in the causation of MS. Stein et al. (27) reported that for over a decade more cases of MS were diagnosed in employees at a Rochester, NY, manufacturing plant that used zinc as a raw material than would be expected to appear in a random population, and suggested that occupational exposure to heavy metals might contribute to the development of MS. Although not well documented in the literature, it is not uncommon to find patients having mercury-based tooth fillings removed once a positive diagnosis of MS has been made.

Vascular

The vascular hypothesis of plaque formation was proposed in 1863 when pathologists noted the close relationship between plaque formation and blood vessels. The vascular hypothesis fell out of favor because of the lack of evidence of vascular thrombosis as the etiology of plaque formation. Suggestions have been made that the vascular hypothesis along with its blood-brain barrier component be reconsidered (5, 18, 19, 26, 28).

Based on the similarity of neurologic features of decompression sickness with those of MS and the supporting literature, James (26) helped revive the vascular etiology hypothesis with the suggestion that the initiating event in MS is subacute fat embolism with damage to the blood-brain barrier. This view has been challenged (29, 30) and responded to (31). James (personal communication) suggested that based on etiology and pathology decompression sickness is a superior model for MS than is EAE.

The vascular ischemic model may be extended by new knowledge of free radicals, with particular reference to their function in reperfusion injury damage (32-35). This new information may also help explain the apparent greater effectiveness in the treatment of MS of the "low pressure" hyperbaric oxygen treatment protocol *(see* below).

Reperfusion injury involves oxygen toxicity. The molecular mechanism(s) of oxygen toxicity is (are) thought to be related to free radicals, partially reduced reactive oxygen species (PRROS). Free radicals are species of atoms or molecules that contain one or more unpaired electrons. These include the superoxide anion radical, peroxide, and hydroxyl radical. PRROS are produced by the sequential univalent reduction of oxygen during aerobic metabolism (32). PRROS have different degrees of reactivity: The superoxide radical serves as a precursor of other reactive radicals and inactivates a variety of enzymes; the hydroxyl radical, the most potent of the PRROS, can react with almost all biological organic molecules, particularly those having unsaturated structures, i.e., unsaturated ring compounds, unsaturated fatty acids, and sulfhydryl groups. By such interactions, the hydroxyl radical can inactivate

enzymes and disrupt membrane components, thereby leading to changes in metabolism and membrane permeability and fluidity (32, 36).

Partially reduced reactive oxygen species are implicated in reperfusion injury and inflammatory processes. Ischemia, irrespective of its cause, has a common outcome, i.e., an interference with tissue perfusion such that the oxygen supply is insufficient to meet the minimum metabolic needs of the tissue. Prolonged interference of energy-producing mechanisms leads to disruption of cell and tissue organization, integrity, and function. More extensive damage may occur when the tissue is reoxygenated upon reestablishment of tissue perfusion. Such additional injury is referred to as reperfusion injury and has been shown to be mediated by the superoxide anion and the PRROS derived therefrom (33, 34). Thus, the efficacy of the Neubauer low-pressure protocol discussed below may be explained by relatively fewer PRROS being formed during his oxygenation procedures-as compared to what may occur with greater focal oxygen tensions due to HBO therapy (HBOT) at higher pressures-thereby limiting if not obviating further damage upon oxygenation.

Inflammation and reperfusion injury may be related to the etiology of MS. Outside the CNS the superoxide formed during the aerobic killing of bacteria by phagocytozing leukocytes diffuses into tissue fluids and reacts with plasma components to produce a powerful chemotactic substance to normal circulating granulocytes. The accumulation of neutrophils at the site of injury and their subsequent activation by ingestion of material from the injury could lead to localized increase of diffused superoxide which, in turn, could lead to further tissue injury, including increased capillary permeability and edema formation. The preceding may explain, in part, the molecular basis for the origin of the MS lesion. The vascular ischemic hypothesis and its molecular basis raises the yet-to-be-answered question as to why there is not a much greater incidence of MS in light of the vast number of known stroke and trauma cases. Here is where knowledge of genetics (predisposition to MS), particular structural-functional "weaknesses" in the myelin of specific neuronal pathways, and neuronal redundancy have to be increased before a more detailed understanding of the etiology of MS will be forthcoming.

However, questions raised about the limitations of the preceding hypotheses suggest that alternative etiologic mechanisms need to be developed. Physiologic mechanisms giving rise to PRROS bring to the fore a new hypothesis, also associated with the relationship of the MS lesion with the venous circulation. Kontos (34) reviewed the evidence related to the cerebral arteriolar dilation, their pathologic sequelae, and their biochemical changes associated with acute hypertension: he especially emphasized the source, formation, and role of oxygen radicals. This is not to imply that systemic hypertension as currently understood is causal to MS. There is no evidence that MS patients have hypertension to any greater degree than the rest of the population. However, insight may be derived from an analogy with low-tension glaucoma,

use of azathioprine (Imuran) also increases the risk of malignancy (44). Yet so powerful is the thinking concerning an immunologic etiology of MS that even authors (43) with statistically insignificant results still conclude: "Nevertheless, our observations suggest that the principle of immunosuppressive treatment in MS is valid and that improvements of the immunosuppression regimen may lead to improved clinical results."

Co-polymer 1 (COP 1; 45), a synthetic polypeptide, may be useful as a therapeutic .agent primarily in the early stages of the exacerbating-remitting form of the disease. The importance of this observation will become apparent when discussing hyperbaric oxygenation.

Plasmapheresis

Plasmapheresis, an expensive therapeutic modality, is based on the presumption that MS is an autoimmune disease and that beneficial effects should be realized through plasma exchange, because any supposed autoantibodies or other immunologically active factors in plasma will be removed. It is ineffective in modifying the course of the disease (3, 46).

Hormonal

Adrenocorticotropin and corticosteroids presumably affect recovery from acute relapses of MS, either by their anti-inflammatory or immunosuppressive actions or both. In a double-blind, placebo-controlled study, Stefoski et al. (47) demonstrated that a mannitol-induced osmotic diuresis clinically improved critical flicker fusion frequency and visual acuity in patients with exacerbating MS, thereby suggesting that steroids function by reducing edema in acute lesions.

The above observation serves as an important transition from the prevailing hypotheses concerning the etiology and pathophysiology of MS to the use of hyperbaric oxygenation.

HyperbarIc Oxygen Therapy

When HBOT was first used for the treatment of MS, there was an immediate negative reaction by neurologists and hyperbaricists. Since 1978, there has been a continuing controversy concerning HBOT's efficacy. At first there was a failure by investigators to provide a scientific rationale for its use, and its use appeared to be contrary to what could be deduced from accepted hypotheses concerning the etiology of MS.

Indeed, in March 1981, Dr. Charles Shilling, then the Executive Director of the Undersea Medical Society, Inc., and Marie Talley published a white paper on the use of HBOT in the treatment of MS as a report to the National Center for Health Care Technology. At that time, MS was classified in category IV of the classification scheme devised by the Hyperbaric Oxygen Therapy Committee of the Undersea Medical Society in its annual report. (The first sentence

of the Committee's description of category N reads: "Disorders for which only hearsay evidence that HBO is of any benefit or for which no theoretical basis for treatment exists are combined in this category.") Shilling and Talley wrote the following concerning the rationale for treating MS with HBO: "There is no known scientific rationale for the treatment of multiple sclerosis in the hyperbaric chamber. There is insufficient evidence to demonstrate at this time that multiple sclerosis should respond to increased partial pressures of oxygen. No theoretical mechanism has been advanced. The committee is aware of a controlled study currently underway. When the data are reported, it (sic) will be evaluated by the medical/scientific community and the committee will consider the reassessment of categorization."

The second sentence of the description of category N states in part, "It is conceivable that some disorders in this group may some day be found to benefit from hyperbaric oxygen therapy."

It is our contention that since the previous assessment, the considerable body of data published deserves critical analysis to determine the efficacy of HBO as a therapeutic modality for MS. It is our intent to state the nature of the controversy surrounding HBO in MS and to critique the double-blind studies published to date that are used to support the contrasting views. It should be noted that several of the publications are difficult to examine in detail because they appear only as abstracts; the full papers are not available despite the fact that their negative results received wide publicity.

The first reports on the efficacy of HBOT in MS appeared in the European literature (48, 49). The effect was discovered independently and confirmed in the United States by Neubauer (50, 51) when, in 1975, he administered HBO to a patient with osteomyelitis who also had MS: the MS markedly improved during the course of therapy.

These reports resulted in two major developments: a) a reassessment of the ways oxygen could influence the disease process and b) the design and execution of the first double-blind study.

In describing the MS lesion, Waksman (2) stated that ". . . hyperbaric oxygen may affect any of a number of the features of the MS process. It is somewhat immunosuppressive and in effective in inhibiting EAE. It affects local tissue oxygenation and thus might diminish the effects of local inflammation leading to myelin breakdown or inhibiting myelin repair."

Oxygen exerts immunosuppressive effects in tissue culture, in EAE in animals, and in MS (52-56) and it may reduce the edema and blood-brain barrier dysfunction, which are well-recognized features of the disease (57).

Much evidence is available from clinical and animal studies indicating that HBO, as a result of its vasoconstrictive actions and improvement of tissue oxygen tension, controls focal edema of decompression sickness: It effectively reduces the raised intracranial pressure associated with global cerebral edema following head and spinal cord injuries and controls edema in traumatic and nontraumatic syndromes: It reduces the pressure in compartment syndromes,

a solid scientific basis for the use of HBOT in MS. Evidence from double-blind studies readily supports the conclusion that HBOT is beneficial in the treatment of MS, especially in its early stages, and is particularly useful for improving bladder-bowel and cerebellar functions.

The significance of improved bladder function is stated by Hallpike (85): "Mitigation of the complications of MS, that is the neurogenic bladder, tremor, and spasticity, and the wider question of rehabilitation are of great practical importance in patient care...."

A critical review of the studies indicates that the data are being evaluated emotionally and not scientifically (62, 63, 65). For example, when Barnes et al.'s (73) paper was published it was given extensive publicity in the United States despite its numerous shortcomings, noted in this critique. As soon as the paper was published, the editor received several letters pointing out some of the shortcomings in the study *(Lancet,* Letters to the Editor, 9 March 1985) These comments were never publicized. In the summary of the Barnes et al. (73) paper one finds the following: "Such a degree of improvement can also be achieved by medication for urinary symptoms, but none of the patients in this study received such medication." One wonders why that statement was included and why the editors permitted it, especially since, as the authors admit, there is no evidence in the paper to substantiate this claim. This statement follows a definitive claim that HBOT improves bowel-bladder function and it precedes the illogical conclusion that their data do "not support the claims made for hyperbaric oxygen in the management of Multiple Sclerosis."

Many questions that may never be answered arise from the results of Barnes et al. (73). However, the publication of such a study has influenced others. For example, the discussion by McLeod (90) following the Wood et al. study (78) is obviously written by someone knowledgeable about MS but apparently not about experimental design of hyperbaric studies and the interpretation of data. The author is either unaware of the successful clinical uses of HBOT or chooses to ignore the pertinent available information. There is no discussion of the shortcomings of the Wood et al. (78) study nor is there an acknowledgment of the limitations of the Barnes et al. (73) study, even though the information is available. It is noteworthy that this very uncritical and negative discussion dwells on side-effects of HBOT, in part based on the work of Barnes et al. After millions of man-hours of exposures throughout the world, side-effects have proven to be minimal when HBO is administered properly (61). Yet no mention is made of the more dangerous and lethal side-effects of alternative chemotherapies even when they are administered properly.

Following the publication of the Wiles et al. study (79), a review, a discussion paper, and several letters to editors of journals appeared (30, 31, 61, 83, 87, 91, 92). Bolt et al. (82) and James (83) criticized the technical aspects of the Wiles et al. study and the conclusions drawn. Bolt et al., as noted above, also

a condition in which apparently "normal" ocular tensions produce increased pressure on the optic nerve and retinal vessels to an extent that axoplasmic flow is interfered with and retinal perfusion is markedly reduced, producing ischemia and tissue hypoxia (37, 38). In such a condition, pressures that are nonpathologic in the vast majority of the population are pathologically high for a very low percentage ofthe population. One can conceive of a similar situation occurring in the cerebral circulation. Systemic pressures that normally would not be considered hvpertensive could cause an arteriolar dilation and free radical formation, vascular injury and edema formation. Also, activation of arachidonate metabolism (34) could lead to thromboxane (TxA2) production. TxA2 is a very potent venous constrictor. The venous constriction could lead to further vascular injury on the venous side-including trapping fat emboli-with the resultant pathology associated with MS. The hydrostatic pressure resulting from focal edema would exacerbate tissue ischemia by mechanical closure of the thin-walled venules. In most cases arteriolar involvement is uniform, but there are occasions when the involvement is nonuniform; in such cases the localized dilatations of the arterioles resemble microaneurysms, or dilated segments alternating with constricted segments (34). Such nonuniformity could help explain the focal nature of MS lesions.

Therapeutics

A variety of 'rational and irrational therapies have been proposed and used for treating MS. Most therapies evolved empirically, some were transferred from diseases considered to be similar in nature, others were unsubstantiated or based on specious reasoning, and some followed the scientific fads of the day (2, 3, 39). Each of these enjoyed a period of enthusiasm and to varying degrees were embraced by medical practitioners, only to be found ineffective.

For the past several decades the most accepted therapeutic approaches to the treatment of MS have been and are based on the infectious-autoimmune model of pathogenesis.

Antiviral Agents

in view of the absence of direct evidence for a viral etiology, it is not surprising that antiviral agents have been ineffective therapeutic agents. However, most antiviral agents are new and either have not been tried in MS or are in the process of being tested.

Immunosuppressants

The autoimmune hypothesis has spawned several immunosuppressive approaches to the treatment of MS: these agents, including ACTH and cortisone, which seem to accelerate recovery from acute relapses, are ineffective in altering the long-term course of the disease (15, 40-44). It should be recalled that cyclophosphamide is a known carcinogen, and that long-term

overcomes the ischemia of cardiovascular accidents and assists in the healing of burns, problem wounds, and skin grafts (58, 59). Its twin abilities of reducing edema and providing oxygenation make oxygen a therapeutic agent superior to an osmotic diuretic such as mannitol (47) and, along with its anti-inflammatory actions and negligible side-effects, theoretically make it superior to ACTH and cortisone. In a head-to-head comparison, Frey et al. (60) found HBOT to be therapeutically equivalent to ACTH in treating MS. The relative absence of side effects (61) supports the conclusion that HBOT is a safer and better method of treatment.

Yet despite the availability of a sound theoretical base and supporting animal and clinical data, the use of HBO in MS is still considered controversial. Nonscientific aspects of the debate have surfaced in magazine and newspaper articles, and noncritical comments condemning its use have appeared in general medical articles (62-65).

To adequately explain the controversy it is necessary to consider many factors, including patient selection, methods of assessment, the type of chambers and pressures used, and the duration and pressure of treatment. Also important are the total number of treatments, booster treatments, and whether long-term follow-up treatments and observations were involved. The patient's alveolar and arterial oxygen tensions during treatment are relevant, as are other therapies, used. Seasonal and ambient environmental factors may also influence therapy. Most of the above issues will be discussed during the critique.

There are at least three major problems in MS research: the absence of a good early diagnostic test, the absence of a quantitative assessment of improvement, and, despite the EAE model, the lack of an animal model.

Early published reports on the beneficial effects of HBOT on MS were anecdotal and did not use double-blind or controlled techniques (48-51, 66). There were few longitudinal studies. Despite these reservations the reports were encouraging and stimulated further research.

The first double-blind study was that of Fischer et al. (67). To date, the studies of Harpur et al. (68), Oriani et al. (69), and Lhermitte et al. (70) are the only ones to have 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 status score. However, Harpur et al. (68) used more disabled, chronic stable patients (Kurtzke >VI). Some of the other published double-blind studies had the patient groups roughly matched, but not the individual patients.

Fischer et al. (67) reported that HBOT (2.0 ATA once per day for 90 min, 5 d/wk, 20 treatments) resulted in objective improvement in mobility, fatigability, balance, and bladder function in 12 of 17 patients. Patients with a less severe form of the disease had a more favorable and long-lasting response. In contrast, only 1 out of 20 placebo-treated patients showed a favorable response. A 1-yr follow-up revealed that only 2 patients in the oxygen-treated

group, neither of whom had an initial positive response, showed signs of deterioration, whereas 11 patients in the placebo group, 1 of whom had a positive initial response, showed deterioration. The 1-yr follow-up results are rather surprising since they occurred without the benefit of additional or continuation treatment.

Being the first double-blind study and reporting highly significant results, the Fischer et al. (67) study serves as a benchmark for the assessment of other studies. It also set one unfortunate precedent: the investigators did not use booster treatments. Based on further experience with HBOT in MS and other disorders, it is somewhat unrealistic to expect a set number of treatments, just 20 in the case of MS, to provide long-lasting benefit.

Arterial Oxygen Tensions

Although the study by Fischer et al. (67) was done at 2.0 ATA in a multiplace chamber, the blood gas measurements indicated that breathing oxygen through a mask resulted in an effective average alveolar Po_2 of 1.3 ATA with a range of 1.1 to 1.5 ATA. This range of arterial oxygen tensions is the same as that suggested in the original protocol by Neubauer (51).

With the exception of a few studies (68, 71), most subsequent investigations were done at 2.0 or more atmospheres of pressure with arterial oxygen tensions in the range equal to or greater than 1.8 to 1.9 ATA (72-79). Such oxygen.tensions are considerably higher than those recommended by Neubauer (51) and higher than those used by Fischer et al. (67) Physiologic, pathologic, and clinical sequelae may vary markedly depending on the P_{AO_2}, and the duration of exposure (80). Whether MS is a disease that is sensitive to the P_{AO_2}, remains to be proven; the current evidence indicates that MS therapy may be oxygen sensitive. Neubauer (51) recommends a need to start therapy using the low-pressure protocol; oxygen tension to be increased gradually over days or weeks with the maximum tension determined by patient response. This procedure is supported by objective neurophysiologic data (14,81) and by theoretical considerations concerning the formation of PRROS discussed above. Relatively fewer PRROS may be formed at the lower oxygen tensions, whereas the deterioration of patients under the high oxygen tension protocol may be due to an overproduction of PRROS producing effects similar to those seen in reperfusion injury.

The relative failure of the Barnes et al. (73; PAO_2 = 1.8 ATA) study and its companion study by Wiles et al. (79; Pa_2, = 2.0 ATA), and the apparent failure of other double-blind studies (75, 76, 78) to duplicate the findings of Fischer et al. (67) and others (49, 66, 82), may in part be related to the failure of these investigators to use the low oxygen pressures advocated by Neubauer (51).

Perrins, a co-author of one of the aforementioned "negative" papers (75), wrote "You must not be surprised when you read our Swedish paper in the BMJ Neurosciences Journal which is now `in print.' I decided to let them put my name on the paper as the work was carefully done and supports your

contention that 2.0 ATA in small chambers as a routine is hardly worthwhile. We continue to get satisfactory responses at lower pressures. But top-ups are essential to maintain improvement in many of the patients" (personal communication to RAN, December 1984). Bolt et al. (82) reports ". ..Wiles and colleagues ... confirm once again that hyperbaric oxygen administered at 2 atmospheres absolute ... is of little value for most patients with multiple sclerosis .... Action for Research into Multiple Sclerosis ... has in the past few years treated over 4000 patients with hyperbaric oxygen in its therapy centers throughout Britain. Until recently about 70% of patients were found to benefit, but experience has shown that if the pressure is adjusted to suit the patient nearly all will respond."

Wiles et al. (79) report that "One patient, whose condition deteriorated dramatically in the month after treatment with hyperbaric oxygen (2.0 ATA) so that she could not walk at all, went to have treatment with hyperbaric oxygen elsewhere ... her condition improved rapidly after this second course of treatment." James (83) states that this patient was "treated with hyperbaric oxygen at lower pressure in an ARMS centre after a relapse." Whereas James ascribes this improvement to the lower pressure regimen, which is consistent with other findings, Wiles et al. (79) imply that this was a placebo effect.

Studies in which lower oxygen tensions were used and no beneficial effects were noted (68, 71) may be explained by other factors pertaining to experimental design discussed below.

Experimental Design

Patient Selection: James (83) suggests that patients with high Kurtzke disability status scores cannot be expected to show improvement, as scar tissue is nonfunctional. He further states: "It is surely time to admit the intellectual bankruptcy of current dogma in this disease and admit that the terms 'multiple' and 'sclerosis' are not a diagnosis. They are a description of an incurable scarring in the nervous system. We need to remove the ridiculous and self-defeating requirement for multiple lesions to be present before trials of therapy can be undertaken."

Harpur et al. (68) claim that low pressures of oxygen have no beneficial effects on chronic stable MS patients; these data are actually at variance with the uncontrolled trial of Harpur and Suke in which 36 of 46 (78%) patients out of 75 who responded to a questionnaire claimed to have derived benefit. There is no current treatment for chronic stable MS patients. The claims for the beneficial effects of HBO are made primarily for chronic progressive patients (82) especially of those with low Kurtzke scores. The Harpur study used patients with Kurtzke scores equal to or greater than VI, where expectations must be limited.

Patients with advanced disease were also used in other studies (70, 71, 73-76,78,79). Hart et al.'s (71) choice of chronic progressive patients with Kurtzke grade VI scores was challenged (84).

When selecting patients one should recall the conclusions of Fischer et al. (67) that ". . . those with less severe forms of the disease had a more favorable response." Hallpike (85) analyzed new treatments for MS and concluded that: "The best prospects for treatment are in the early stages of the disease. . . ." Murthy et al. (77) report: "Overall results showed no statistically significant findings in various subsets between the two groups. However, when patients with only low Kurtzke grades (VI or less) were considered, seven of nine patients improved significantly, whereas none of the placebo group improved .... Future HBO studies will be targeted toward mild to moderately involved MS patients." The aforementioned conclusions concerning the use of COP I in early MS should be recalled.

Duration of Treatments: In their initial studies Barnes et al. (73) and Wiles et al. (79) used 20 treatments with either limited or no long-term follow-up to determine whether there were delayed effects of HBOT as had been reported by others. However, the final report by Barnes et al. (86) states that the oxygen-treated group shows subjective improvement of bladder function for 6-12 mo. without any continuation therapy, and that there is significantly less deterioration in cerebellar function at the end of the 1-yr follow-up. Similar beneficial results were reported by Oriani et al. (69) in their 1-yr study, which included monthly, 5-d booster treatments.

Controls: Despite the availability of discussions concerning proper controls in HBOT experimentation (80), few investigators have used 1 ATA oxygen as a control. This is an indispensable control because it provides the basis for the need for higher oxygen pressures.

With respect to pressure controls, some investigators have used a mixture of 10% oxygen:90% nitrogen at 2 ATA (67, 76, 78) or 12.5% oxygen at 1.75 ATA (68); these are appropriate pressure controls: other investigators did not have appropriate pressure controls (71, 73, 75, 79).

For example, in two major studies (73, 79), which claim to prove conclusively the inefficacy of HBOT in MS (87), an inappropriate 1.1 ATA (for a 2 ATA experiment) pressure control was used. The 0.1 ATA over pressure is insufficient to obtain comparative dysbaric effects in the experimental and the placebo groups. This is why the patients in the placebo groups did not experience barotrauma of the same degree as was reported for the experimental groups. These investigators had an unacceptable high incidence of barotrauma in the treated group, which casts a negative reflection on the apparent quality control of the pressurization-decompression procedures to which they subjected their patients: their conclusions concerning the side effects of HBOT are of little clinical value and significance.

Analysis and Misinterpretation of Data

Harpur et al. (68), claiming to disprove earlier reports that magnetic resonance imaging could follow the benefits of HBO objectively, report that there

are equivalent changes in the number and size of lesions in the control and treated patients. These data are at variance with those of Neubauer, Kagan, and Gottlieb (presented at three international meetings; paper in preparation). Kagan (personal communication) points out that the equipment used by Harpur et al. (68) is not state-of-the-art: their equipment makes 1.0-cm non-contiguous slices, whereas Neubauer et al.'s equipment makes 2.0-mm contiguous slices: The slices made by Harpur et al. equipment are too large to detect the small changes, particularly those associated with the small, newly forming lesions noted by Neubauer et al.

Barnes et al. (73) appear unable to draw proper conclusions from their data: Their P value of 0.03 with respect to improvement by HBOT on the Kurtzke functional systems scale on the subjective bowel-bladder parameter is the same level reported by Fischer et al. (67). Yet they conclude: "The short-term results of this trial do not support the claims made for hyperbaric oxygen in the management of multiple sclerosis."

Neubauer's uncontrolled studies (88) reporting positive effects of HBOT on bladder function have been confirmed by others in double-blind studies (63, 67, 73, 74), including studies using sophisticated urodynamic measurements (72). Not all investigators find positive results using quantitative measurements (79). James (personal communication) recalculated the statistics reported by Wiles et al. (79) and found a significance of 0.03 rather than the reported 0.07 that Wiles et al. claim represents "a trend in favor of the group given hyperbaric oxygen that was just short of significance." A careful review of the literature reveals that bladder and bowel functions are the two problems most amenable to HBOT; they seem not to be particularly sensitive to the increased oxygen tensions as are disorders of the CNS. Such an observation may be congruent with the knowledge that the evolutionally older parts of the CNS tend to be more resistant to hypoxia and various drugs, i.e., alcohol, than the evolutionally newer neocortex and diencephalon.

Rosen (89) concludes that his uncontrolled data indicated "that HBO has no objective benefit in the treatment of moderately advanced multiple sclerosis." Yet he reported that 67% (8 of 12) showed improvement in urinary urgency and incontinence.

Comments on the Controversy

A critical review of the data indicates that the infectious-immunologic model of the etiology of MS leaves much to be desired. Despite the expenditure of many millions of dollars in the investigation of this model, the medical and scientific communities are no closer to a definite understanding of the etiology or to an effective therapy based thereon. There is a growing opinion of the need for a new approach to research in MS, and excellent competing approaches are worthy of further study. Vascular models provide the fundamental understanding of the underlying pathophysiology of the disease process, and give

provided preliminary data of their long-term longitudinal studies demonstrating positive effects of the low-pressure protocol on chronic progressive MS.

Mertin and McDonald (93) reviewed the use of HBOT for MS without waiting for the final reports of some of the studies discussed. They negatively reviewed the underlying basis for HBOT and emphasized possible adverse side-effects. The positive Fischer et al. (67) study was negatively reviewed, whereas the markedly flawed negative study of Barnes et al. was not criticized. Davis (61), Neubauer (92), and James (91) responded to this biased review, with Davis pointing out the marked safety of HBOT as a therapeutic modality, and James pointing out the factual errors and uncovering an important conflict of interest of one of the authors relating to his investment in a competing therapy.

Bates (87), an author of the Barnes et al. study, published a dismissive discussion paper concerning the use of HBOT in MS. His analysis criticized published papers except his own and the companion Wiles et al. (79) study. It included disparaging remarks about the honor and integrity of the officials and scientists of ARMS, an organization providing low-cost HBOT for MS patients in Great Britain. Bates stated: "The recent publication of negative results in the second large double-blind controlled trial of hyperbaric oxygenation in multiple sclerosis (MS) in Britain [referring to Wiles et al.], confirming those reported in the early part of 1985 from the Newcastle Group [referring to Barnes et al.], would appear to refute once and for all the suggestion that hyperbaric oxygen has any role to play in the management of patients with MS .... Yet once again the results have been criticized in the lay press by members of the medical profession...." There was no recognition of the criticism in the scientific and medical literature, especially of the study in which he was involved.

Bates questioned the intentions and motives of those involved with ARMS: "The question arises as to why the proponents of hyperbaric oxygenation should be so insistent upon their claims that the treatment is of benefit to their patients. There is of course, the inevitable fact that the provision of these chambers throughout the country represents a significant investment in personal effort, time and money which it will be so hard to accept has been fruitless." He reluctantly admitted that ". . . there are also significant numbers of patients who have not provided the initial capital investment and yet who feel that they have benefited from the treatment." Indeed, contrary to Bates' ad hominem attack, ARMS is very concerned about learning the truth about the efficacy of HBOT in MS, and, as mentioned above, the long-term longitudinal studies that are emerging from the ARMS centers (82) strongly support the conclusion that HBOT is beneficial in MS. One of the ARMS investigators is Perrins, who was a co-author of the negative Neiman et al. (75) study. Perrins has since changed his negative opinion, as described in his letter to Neubauer, in his co-authorship of the letter to the editor with Bolt et al. (82), and in his oral presentations at international meetings. Also, for the past 25 yr Perrins

has been one of the most respected clinical hyperbaric investigators as a result of his seminal work in osteomyelitis and wound healing (59).

With his seriously flawed work as a standard coupled to a negative predisposition to HBOT, Bates (87) ends his discussion: "It is disappointing, but perhaps inevitable, that in this age of improving communications it is still easier to find a publisher for work which suggests a possible benefit for a condition-even when the study is small in size or uncontrolled-than for a more significant but negative study." The irony of all of Bates' negativism is that his final report with Barnes et al.(86) demonstrates that HBO improves cerebellar and bowel-bladder function.

There is need for further research. However, the variable nature of the disease may preclude a large double-blind study because of the increased difficulty involved in matching patients as the size of the study increases. Long-term continuous monitoring of individual patients who serve as their own historic controls, coupled to real-time monitoring of.CNS tissue changes, will provide-at the minimum-the most objective data with which to assess the efficacy of treatment protocols of HBO alone and in combination with other therapeutic agents. Such studies should be carried out with meaningful participation of those who have been successful in treating MS with HBOT.

Conclusions

Of all the current therapies presumably based on an understanding of the etiology and pathophysiology of the disease process, HBOT has the soundest foundation. It is also the safest drug available. It is not surprising, therefore, to find that there is much positive evidence concerning the beneficial effects of HBOT on cerebellar and bowel-bladder function to sanction its use for treating MS. Based on comparative efficacy and safety considerations, it is recommended that HBOT be used for treating early MS and for treating MS-associated cerebellar and bowel-bladder dysfunction.

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