ARTERIAL GAS EMBOLISM AS A CONSEQUENCE OF PULMONARY BAROTRAUMA

Arterial gas emboli may result from arterialisation of venous gas emboli or may be introduced directly into the arterial circulation.[1] Included amongst the latter are divers, submarine escapees, and aviators who develop arterial gas emboli as a consequence of decompression in the absence of a tissue inert gas load that could account for gas emboli production.

THE ORIGINS OF ARTERIAL GAS EMBOLI COMPLICATING DECOMPRESSION

The conventional explanation is that decompression may result in an expansion of intrapulmonary gas in accordance with either Boyle's Law or Van der Waal's equation, sufficient to cause such pulmonary derangement that gas is introduced into the pulmonary vein.[2]

Despite 100 years of research the typical pulmonary lesion underlying the evolution of an arterial gas embolus has not been described. This makes it very difficult to prepare a suitable animal model to study subsequent events.

Few casualties with overt pulmonary damage due to decompression (pulmonary barotrauma) develop evidence of arterial gas embolism, and conversely few casualties suffering from arterial gas embolism have overt evidence of pulmonary damage. In the last 10 years at the Royal Australian Navy School of Underwater Medicine, 21 casualties have been treated for arterial gas embolism and 42 casualties have been treated for overt pulmonary barotrauma. During that time only one casualty has had unequivocal evidence of both arterial gas embolism and pulmonary barotrauma. This negligible overlap is surprising if these two conditions have a causal relationship.

TABLE 1
ROYAL AUSTRALIAN NAVY SCHOOL OF UNDERWATER MEDICINE
SURVEY OF GAS EMBOLISM AND PULMONARY BAROTRAUMA 1975-1983

Arterial Gas Embolism Cases	21
Pulmonary Barotrauma Cases	42
Combination of Gas Embolism and Pulmonary Barotrauma Cases	1

THE BEHAVIOUR OF GAS INTRODUCED INTO THE ARTERIAL CIRCULATION

The distribution of gas introduced into the arterial circulation is dictated by the posture of the diver, submarine escapee, aviator or experimental animals.[3] This explains both the preponderance of neurological involvement in divers and submarine escapees due to their upright posture, and the insistence on maintaining a casualty with arterial gas embolism in the head down/feet up posture.

The cerebrovascular reaction to a gas embolus differs from that to a solid embolus where vasoconstriction is usual, in that the reaction to a gas embolus is generally localised vasodilation.[5,6,7] A significant proportion of gas entering the cerebral circulation will pass through to the venous circulation without causing vessel occlusion.[3,5] Only when gas coalescence occurs to form a gas plug of sufficient size does vascular occlusion occur.[8] This is usually at a vessel bifurcation and in a vessel of 30-60 microns diameter.[8,9] The most plausible explanation of this is that the gas embolus will become stationary when the frictional forces that exist between the gas and the vessel exceed the local systemic driving pressure.[8]

THE PATHOLOGICAL SEQUELAE OF GAS EMBOLUS ENTRAPMENT

Once arterial gas emboli cause vascular occlusion, pathological processes are initiated. For the cerebral circulation these have been well defined.[2,5,8,9,17]

TABLE 2
PATHOLOGICAL SEQUELAE OF CEREBRAL ARTERIAL GAS EMBOLUS ENTRAPMENT

Increased blood-brain-barrier permeability

Tissue ischaemia

Downstream vessel coagulopathy

Small focal haemorrhages

Loss of cerebrovascular autoregulation

Metabolic disruptions

An increase in blood brain barrier permeability will result in an increase in brain water content, that is to say brain oedema of a vasogenic nature.[10,12] The rate of development of this brain oedema is critical to a major controversy in the treatment of cerebral arterial gas embolism. The rate of oedema accumulation following gas embolus entrapment is dependent upon whether the experimental animal is recompressed.[18] Human data is not available. If the animal is untreated, then oedema accumulates over several hours, but most studies have displayed negligible oedema within the first hour after embolisation.[10-12] Treatment of the animal by recompression appears to either prevent or retard the development of oedema.[18]

Other sequelae include tissue ischaemia which may result in infarction,[2,5,11,13] endothelial oedema and formation of platelet thrombi causing progressive vessel occlusion,[8,14,15] small focal haemorrhages,[9] and cellular metabolic disruptions.[11] The reported loss of vascular auto regulation has not been established experimentally. The vasoreactivity of a vessel adjacent to a gas embolus is unknown and is an area of active research within the Royal Australian Navy because of the current recommendation to use vasoconstricting gas mixtures.[19] If the vessel adjacent to a gas embolus is vasocreactive then vasoconstricting gases should initially be avoided as any vasoconstriction will

inhibit redistribution of the embolus by increasing both the gas-vessel interface and the frictional forces that oppose embolus movement.

PHENOMENA THAT MAY CONTRIBUTE TO THE CEREBRAL LESION

Any underlying pulmonary lesion and any cardiac involvement may contribute to cerebral pathology. While most theorists propose that pulmonary barotrauma underlies the evolution of arterial gas emboli, they also assume that the pulmonary lesion does not contribute to the evolving cerebral pathology. Possible ways in which any pulmonary lesion might contribute to cerebral pathology include systemic hypoxia, release of vasoactive substances stores in the lungs, impairment of venous return by expanding mediastinal gas, and most importantly, by continuing to introduce gas into the pulmonary vein. If any communication exists between the airways and the pulmonary vein, continued embolisation will result as a consequence of the pressure differential between them.[3]

THE EFFECTS OF RECOMPRESSION

Given a surface tension of 47 dynes/cm for plasma, thermodynamic theory predicts, for a typical gas embolus occupying a vessel of 30 to 60 microns diameter, that compression from 1 Ata to 6 Ata will not force the gas embolus into solution.[20] Nevertheless if a casualty with a cerebral arterial gas embolus is recompressed with minimal delay from onset of symptoms and signs, as in the Submarine Escape Training Tank (SETT) at HMS DOLPHIN, almost all casualties achieve dramatic total relief.

TABLE 3
TIMES FROM THE ONSET OF COMPRESSION TO TOTAL RELIEF OF SIGNS AND SYMPTOMS

Time in Minutes	Cases
less than 1	42
1 - 5	30
6 - 30	8
31 - 120	2

In the 112 cases of cerebral arterial gas embolism recorded at HMS DOLPHIN the time from the start of compression to the time of total relief was determined where possible. For 20 cases this was not recorded clearly. Three cases obtained no relief and died. Another 7 cases obtained total relief only after decompression from 50 msw. The remaining 82 cases obtained total relief before decompression.

Such rapid total relief can only be explained by redistribution of the gas embolus as a result of reduced gas-vessel interface frictional forces.[6,8,9] Of note is the finding that after recompression of embolised rats to 6 Ata, 30-40% of the gas redistributed to other parts of the brain.[6] This is one mechanism that can explain those casualties who relapse with different symptoms and signs from their initial presentation.

THE PATHOLOGY OF RELAPSE

Following the dramatic recovery of nearly all casualties treated without delay, some casualties either relapse or deteriorate. For most groups studied, whether they be submarine escapees or divers, the proportion relapsing is about 30%. Of this group about 5 to 10% die, contributing to the overall mortality of cerebral arterial gas embolism which even in the best circumstances is about 5%.[14,19,21,31]

Numerous pathologies have been proposed to explain these casualties that relapse or deteriorate.[2,4,6,8,10-12,14,15,21,30,31] Re-embolisation may result from redistribution of a cerebral arterial gas embolus to another region of the brain, redistribution of gas from elsewhere in the body to the cerebral circulation, for example, with a change of posture, or as a consequence of continued embolisation from an original pulmonary lesion.[32]

TABLE 4
PROPOSED CAUSES OF RELAPSE OR DETERIORATION AFTER RECOMPRESSION

Re-embolisation

Regeneration of gas volume

Focal brain oedema

Failure of re-perfusion

Others

Careful examination of the literature and casualty case reports indicates that no single proposed cause of relapse can explain the majority of cases that relapse or deteriorate after initial improvement[2,4,6,8,10-12,14,15,19,21-31]. This contrasts with the recent proposal that brain oedema is responsible for the majority of cases that relapse and that treatment of a relapse should consist of increased “brain-oedema” therapy and not recompression.[19,21,30,31] Much of the evidence for this proposal comes from case report symptomatology.[30,31] However, brain oedema is a pathological and not a clinical diagnosis, as there is no symptom complex indicative or typical of brain oedema.[32]

There is other evidence against brain oedema as the major cause of relapses. First, brain oedema is related to the original site of the cerebral arterial gas embolus and cannot account for those casualties that relapse with totally different symptoms from the original presentation (Table 10).[19] Second, the rate at which brain oedema develops and resolves is incompatible with those casualties that relapse dramatically during decompression and respond immediately to recompression. This phenomenon is demonstrated by the data from the SETT at HMS DOLPHIN displayed in Table 5. These were 32 casualties of whom two relapsed twice so giving a total of 34 relapses.

Note that 14 cases relapsed either during or within 5 minutes of decompression to a shallower depth. Of the 16

TABLE 5
ONSET OF RELAPSES AND THE RESPONSES OF RELAPSES RECOMPRESSED IMMEDIATELY

Time of onset of relapse or deterioration	While at 50m	During decompression to a shallower depth	Minutes after arrival at a shallower depth					
			0-1	1-5	6-11	11-15	16-30	More than 30
Number of relapse cases	5	6	3	5	4	1	3	7
Number of cases recompressed immediately after a relapse	0	3	3	5	3	0	0	2
Number obtaining immediate total relief with recompression	-	2	1	1	0	-	-	1
Number obtaining total relief within 10 minutes of recompression	-	0	0	3	3	-	-	0
Number obtaining total relief more than 10 minutes after recompression	-	1	1	1	3	-	-	1

Five cases relapsed or deteriorated while the casualty was at 50msw. The remaining 27 cases relapsed or deteriorated during or after decompression. Two cases relapsed twice giving the total of 34 relapses in this table. Sixteen of the 27 cases were recompressed as soon as the symptoms or signs of the relapse or deterioration became apparent. The responses to recompression are also detailed.

TABLE 6
TIME FROM ONSET TO RELAPSE IN HOURS

Hours from Onset to Relapse	No. Cases
Less than 1	14
1 - 2	5
2 - 3	2
3 - 4	1
4 - 5	1
5 - 6	1
6 - 7	0
Greater than 7	2

In 6 of the 32 cases of relapse the time from onset to relapse was not clearly recorded.

TABLE 7
TIME FROM ONSET TO RELAPSE IN MINUTES

Hours from Onset to Relapse	No. Cases
Less than 20	2
20 - 40	9
40 - 60	3
60 - 90	3
90 - 120	2

These cases appear in the "less than 1 hour" and "1 to 2 hours" classifications in Table 7.

casualties who relapsed and were recompressed within 5 minutes of the onset of the relapse, 8 obtained total relief from the relapse within 10 minutes of recompression and a further 7 obtained relief which was complete more than 10 minutes after recompression. Another 6 cases not recorded in Table 5 were recompressed after they relapsed, but recompression began more than 5 minutes after the onset of the relapse. Of this group, 5 recovered rapidly after recompression and 1 recovered gradually but eventually completely.

Third, as discussed, even for untreated experimental animals negligible brain oedema accumulates during the first hour after embolisation.[10-12,18] It follows that brain oedema cannot account for the peak occurrence of relapses and deteriorations at 20 to 40 minutes after the initial presentation for the 32 casualties that have relapsed or deteriorated after initial improvement at HMAS DOLPHIN.

Clearly brain oedema is a complication of untreated cerebral arterial gas embolism. However it does not provide a good explanation of the majority of cases that relapse or deteriorate, and consequently "brain-oedema" therapy is not an adequate response to all relapses or deteriorations. There are numerous possible causes of relapse or deterioration after initial improvement and the clinical response to a relapse or deterioration must be dictated by both the circumstances in which the relapse occurred and by the nature of the relapse.

THE CLINICAL PRESENTATION OF CEREBRAL ARTERIAL GAS EMBOLISM

The symptomatology from the HMS DOLPHIN cerebral arterial gas embolism cases are typical of other reports and are listed at Tables 8 and 9.[4,28,29]

TABLE 8
PRESENTING SYMPTOMS AND SIGNS OF 112 CASES OF CEREBRAL ARTERIAL GAS EMBOLISM

Unconsciousness	45
Sensory loss	25
Paresis	24
Stupor	22
Collapse without unconsciousness	13
Visual disturbances	10
Convulsions	4

TABLE 9
PRESENTING SYMPTOMS AND SIGNS OF THE 32 CASES THAT RELAPSED AFTER INITIAL IMPROVEMENT

Unconsciousness	14
Sensory loss	5
Paresis	7
Stupor	7
Collapse without unconsciousness	4
Visual disturbances	2
Convulsions	1

Note the common symptom frequency distribution for all cases and for those cases that relapsed and that it is therefore impossible to predict which cases will relapse or deteriorate on the basis of their presenting symptoms and signs.

In contrast, for the casualties that relapsed, the symptom frequency distribution at initial presentation and at relapse are different.

TABLE 10
SYMPTOMS AND SIGNS ON PRESENTATION AND RELAPSE

Symptoms and Signs	Initial Presentation	Relapse
Unconsciousness	14	2
Sensory loss	5	7
Paresis	7	7
Stupor	7	6
Collapse without unconsciousness	4	0
Visual disturbances	2	9
Convulsions	1	6

32 patients relapsed following improvement. Some casualties presented with more than one symptom or sign, either initially or on relapse.

This is relevant to focal pathologies proposed as causes of relapse or deterioration. Any pathology that is related to the original site of the cerebral arterial gas embolus such as brain oedema, regeneration of gas volume, and failure of reperfusion due to progressive vascular occlusion should result in a relapse that is similar to the initial presentation.

GENERAL COMMENTS ON THE TREATMENT OF CEREBRAL ARTERIAL GAS EMBOLISM

Most discussions of the treatment of cerebral arterial gas embolism do not differentiate between SETT casualties and divers. This a major oversight as the two groups are significantly different.[33] SETT casualties have a negligible increase in tissue inert gas content. In contrast divers have a variable but significant increase, particularly when it is remembered that the half life for uptake of inert gas by the brain is only 5 minutes. The inert gas elimination kinetics are totally different for these two situations. Cerebral arterial gas embolism is most frequently encountered in sports divers, who, rarely having a recompression chamber at their diving site, rarely present for treatment within 1 hour, in contrast to SETT casualties who are recompressed immediately their symptoms develop.

These observations illustrate the difference between SETT casualties and divers with cerebral arterial gas embolism, the inappropriateness of combining data from divers and SETT casualties as has been done by many authors,[30,31,34] and why the Royal Australian Navy is developing different animal models to evaluate the treatment needs of these two situations.

Another major treatment concept is that any delay in recompression will result in increased morbidity and mortality.[19] There are no controlled human studies to support this. Sufficient numbers of otherwise homogeneous cases for comparison can only be generated by review of SETT casualty case reports. In this assessment the relapse rate is used as the indicator of success or failure. Although the data displayed suggests that any delay may lead to a worse outcome, the difference displayed for these two groups is too small to establish statistical significance. Nevertheless it is reasonable to accept that until better data is available the time from onset of symptoms to recompression should be minimised.

TABLE 11
THE RELATIONSHIP OF DELAY IN COMPRESSION OF THE CASUALTY TO 50 MSW TO RELAPSE

Time from onset of symptoms to arrival at 50 msw in minutes	Total Number	Relapse Number	Relapse Rate
Less than 582	22	27%	
5 or more 19	7	37%	

The time interval from the onset of symptoms and signs to compression of the casualty to 50 metres was evaluated in all 112 cases. For 1 case the time taken to reach 50 msw was not recorded clearly. This casualty did not relapse. Another 7 cases were compressed to depths other than 50 msw. Three of these 7 cases relapsed. Three other cases showed no improvement with recompression and died. The remaining 101 cases are detailed above.

THE TREATMENT DEPTH

Current regimens advise compression to 50 msw (165 ft) if treatment is instituted within five hours.[35,36] This is

based on the following. First, although a cerebral arterial gas embolism becomes more spherical with volume reduction, the rate of reduction in gas diameter decreases markedly with increasing depth such that beyond 50 msw considerable further compression is required to produce any noticeable reduction in gas embolus diameter. This does not apply to the same degree to any gas embolus which remains in a cylindrical configuration. Second, animal studies have demonstrated that cerebral arterial gas emboli redistribute with compression to 50 msw, with some embolus redistribution seen at 30 msw (100 ft).[9] Third, significant human data only exists for treatment at 50 msw.[1,37] For example only 7 of the 115 cases from HMS DOLPHIN were not treated at 50 msw. All 7 were treated at shallower depths than 50 msw and 3 of these cases relapsed.

Leitch et als study of embolised rats at NMRL suggests that treatment at 18 msw (60 ft) breathing oxygen might be as good as compression to 50 msw.[18] The study findings conflict with an unpublished study by Bayliss, who decompressed rats with ligated tracheas and have the serious limitations of any study that uses the technique of direct infusion of gas into the vessels supplying the cerebral circulation. However it does provide support for the widely accepted proposition that if a casualty presents after 5 hours he should only be compressed to 18 msw[35,36] and also provides additional stimulus for the Royal Australian Navy's current evaluation of different treatment depths.

TIME AT THE TREATMENT DEPTH PRIOR TO DECOMPRESSION

During the last 15 years, despite the reports of Elliott, Harrison et al[28] and Ah-See,[4] an increasingly common practice has been to begin decompression from 50 msw after 30 minutes if the casualty is asymptomatic.[9,34,38-40] However comparison of the relapse rates of otherwise homogeneous SETT casualties and the time spent at 50 msw prior to decompression indicates that this practice should be abandoned.

The 16 to 30 minute group was comprised of casualties who were kept at 50 msw for 30 minutes prior to decompression, The 31 to 120 minute group included 8 casualties who were kept at 50 msw for 60 minutes, while the remainder were kept at 50 msw for 2 hours prior to decompression. By X^2 analysis, the relapse rates for these groups are significantly different at the 0.01 level.

Clearly casualties kept at 50 msw for only 30 minutes have a significantly greater relapse rate than those kept at 50 msw for either 1 or 2 hours. Decompression from 50 msw should not begin after 30 minutes, and probably a casualty should be kept at 50 msw for as long as possible while still maintaining access to a conventional therapeutic table. If the therapist has access to therapeutic tables such as Royal Navy Table 54, then 2 hours at 50 msw would appear indicated.

OXYGEN AT HIGH PRESSURES

Since the introduction of the Goodman and Workmann oxygen breathing therapeutic tables,[41] the concept that "the more oxygen you give, the better you are doing" has

TABLE 12
THE RELATIONSHIP BETWEEN TIME SPENT AT 50 MSW BEFORE DECOMPRESSION AND RELAPSE

Time at 50 msw Prior to Decompression (Min)		Total Number	Relapse Number	Relapse Rate
0 - 15	18	8	44%	
16 - 30	34	12	35%	
31 - 120	28	2	7%	

The time spent at 50 msw prior to decompression was considered for all 112 cases. This time was not clearly recorded in 17 cases, 7 of which subsequently relapsed. Another 7 casualties were recompressed to depths other than 50 msw; 3 of these 7 cases relapsed. Three cases showed no improvement with recompression ad died. Five casualties relapsed at 50 msw prior to decompression. The remaining 80 cases were analysed and are presented above.

crept into underwater medicine folk-law. This has resulted in attempts to increase the inspired partial pressure of oxygen being breathed at 50 msw in the treatment of cerebral arterial gas embolism.[19] It is important to review the reported advantages and disadvantages of breathing oxygen at high pressure.

TABLE 13
REPORTED ADVANTAGES OF OXYGEN AT HIGH PRESSURES

Reduced cerebral blood flow
Increased tissue oxygenation
Reduced blood brain barrier permeability
Positive vascular steal

Reported advantages of oxygen at high pressures include cerebral vasoconstriction resulting in a fall in cerebral blood flow, a fall in intracranial pressure, and therefore increased rate of brain oedema resolution, increased tissue oxygenation, and decreased blood brain barrier permeability.[17,42-44]

TABLE 14
REPORTED DISADVANTAGES OF OXYGEN AT HIGH PRESSURES

Inert gas
Oxygen toxicity
Rebound in brain oedema following withdrawal
Increased blood brain barrier permeability Increased cerebral blood flow

Reported disadvantages of oxygen at high pressure include the observation that if oxygen is supplied in excess of local metabolic needs it will behave as an inert gas, pulmonary and CNS oxygen toxicity, increased blood brain barrier permeability, increased cerebral blood flow resulting in increased intra-cranial pressure, impaired cerebral glucose metabolism, and gas embolus expansion.[5,43,45-52]

The apparent contradictions result from the observation that alteration of the inspired partial pressure of oxygen

can result in a considerably different effect.[42,44,52] If the inspired partial pressure of oxygen is in the 1 to 1.5 ATA range cerebral vasoconstriction, improved cerebral glucose metabolism, and improved EEG recordings are the usual findings. If however the inspired partial pressure of oxygen is increased to and beyond 2 Ata, both cerebral glucose metabolism and EEG recordings deteriorate.[50-52] Also in this range the effects on cerebral blood flow are variable. A particularly common finding is for an immediate increase in cerebral blood flow with a fall towards the previous level over 30 to 40 minutes.[50,51]

TABLE 15
THE EFFECTS OF RAISING THE INSPIRED PARTIAL PRESSURE OF OXYGEN

P_i0_2 in ATA	Glucose Utilization	EEG	Cerebral Blood Flow
1	↑	Improved	↓
1.5	↑	Normalised	↓
2	↓	Deteriorated	↑↓
2.8	↓	Grossly Abnormal	↑↓

It could be argued from this data that the inspired partial pressure of oxygen be maintained within the 1 to 1.5 Ata range. Conveniently this is achieved by breathing air at 50 msw avoiding the need to use a built-in breathing system. The only indication to exceed this range would be to increase the elimination of inert gas. This is not relevant to the SETT casualty but may be relevant to the diver, and is yet another phenomenon being investigated by the Royal Australian Navy. A reasonable regimen would be to administer an inspired partial pressure of oxygen of 1 to 1.5 Ata to SETT casualties, and until further information is available to adjust the inspired partial pressure given to a diver according to his dive profile.

CHEMOTHERAPY FOR CEREBRAL ARTERIAL GAS EMBOLISM

There are no drugs of proven benefit for the primary problem of a gas embolus occluding a vessel although research into the role of heparin, indomethacin and prostaglandin 12 in facilitating reperfusion of the brain after embolus redistribution is having encouraging results. These drugs may become important adjuvants to recompression.[53-58] The use of naloxone and dimethyl-sulphoxide (DMSO) also have support from experimental animal studies.[59,60]

Most forms of chemotherapy suggested for use in the treatment of cerebral arterial gas embolism relate to either preventing or ameliorating the development of brain oedema.[2,13,21,32,48,61-64] The inability to predict which cases will relapse on the basis of their presentation, and the lack of an identifiable brain oedema clinical syndrome, result in the inevitable conclusion that if a prophylactic brain oedema regimen is indicated, it should be given to all casualties.

Although the initial brain oedema complicating cerebral arterial gas embolism is vasogenic, eventually both vasogenic and cytotoxic brain oedema will be present.[13] This places another condition on a brain oedema regimen in that it must include agents active against both forms of oedema. Non-osmotic diuretics, such as furosemide, dexamethasone and phenobarbitone have been shown to be effective in treating vasogenic brain oedema models.[13,32,62,64] Osmotic diuretics, such as mannitol and glycerol, non-osmotic diuretics and methylprednisolone sodium succinate have been shown to be effective in treating cytogenic brain oedema models.[2,13,32,64]

A recent report of the efficacy of a steroid regimen in reducing the relapse rate associated with cerebral arterial gas embolism inappropriately combined diving casualties and SETT casualties to generate sufficient numbers for comparison.30,31 The efficacy of a steroid regimen in treating brain oedema consequent on a cerebral arterial gas embolus is yet to be established. It must be noted that steroid regimens for other causes of brain oedema are falling into disrepute.32,64 It should also be noted that given the wide range of steroidal effects the efficacy or lack of efficacy of asteroid regimen does not implicate or refute any proposed underlying pathology.30,31

Other areas of treatment of cerebral arterial gas embolism include the management of a relapse or deterioration mentioned previously, the possible roles of mechanical ventilation to maintain hypocarbia and in particular high frequency ventilation (HFV), and hypothermia in the management of the critically ill casualty.32,48

CONCLUSIONS

Far from being an area of consensus and understanding, cerebral arterial gas embolism is an area of confusion and active debate. The confusion relates not only to the underlying pathological processes but also to the ideal treatment of cerebral arterial gas embolism affecting divers, submarine escapees and aviators.

ACKNOWLEDGEMENTS

The author wishes to acknowledge the help, co-operation, and advice received from Dr TG Shields, Senior Lecturer in Offshore Medicine, at the University of Aberdeen.

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This paper was presented at the European Undersea Biomedical Society meeting in Bar*celona in September, 1983. We are grateful for permission to publish.*

HYPERBARIC OXYGEN FOR MULTIPLE SCLEROSIS

Philip James

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

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

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

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

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

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