the lack of response to our requests for the data which would prove or disprove the worth of a concept which, despite the obstacles to scientific evaluation, is increasingly being adopted in the United States and elsewhere.

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Occasional Survey

EVIDENCE FOR SUBACUTE FAT EMBOLISM AS THE CAUSE OF MULTIPLE SCLEROSIS

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Summary The neurological features of decompression sickness, which is thought to be due to gas embolism, are similar to those of multiple sclerosis (MS). This similarity suggested the re-examination of a concept, first proposed in 1882, that the demyelination in MS is due to venous thrombosis. Unfortunately, although the plaques of MS are often perivenular, thromboses are not always present. Nevertheless, vascular theories can explain the topography of the lesions in MS. Embolism is generally associated with arterial rather than venous damage, and with neuronal infarction rather than loss of myelin. However, the intra-arterial injection of a range of substances can cause venous damage and perivenous demyelination in the brain, although it does not exactly reproduce the plaques seen in man. There is also evidence in man that fat may lodge in the microcirculation of the nervous system and cause distal perivenous oedema with the loss of myelin from axons. Since acute fat embolism may produce lesions not only in the white matter of the brain, but also in the cord, the retina, the meninges, and the skin, and since all these have been described in MS, subacute fat embolism may be the cause of MS.

INTRODUCTION

THERE is little doubt that the presence of gas in the nervous system causes the neurological symptoms of decompression sickness. Because the commonest neurological symptoms of decompression sickness are dizziness (often accompanied by nystagmus), visual disturbances, impairment of micturition, and weakness of the legs,[1] the condition invites comparison with multiple sclerosis (MS). The other features the two conditions have in common are the often transient nature of many of the cerebral symptoms (although vestibular disturbances may persist) and the tendency of the cord damage to leave permanent disability.

Neurological effects of decompression occur more commonly with diving on compressed-air, than when helium and oxygen mixtures are used.[2] The difference is said to be due to the greater solubility of nitrogen in the lipids of the nervous system, which partly explains why the residual damage occurs almost exclusively in the white matter. Gas that enters the spinal cord during decompression may expand as the diver continues to ascend, causing mechanical disturbance and eventually ischaemia.[3,4] The range of damage caused, which varies from necrosis to loss of myelin,[5] is that which is also found in MS. This similarity has aroused interest in the vascular features of MS.

Most present day accounts describe MS as being simply a disease associated with a patchy loss of myelin in the central nervous system and rarely mention its other features—loss of neurones,[6] involvement of peripheral nerves,[7] meningeal inflammation,[7] retinal changes,[8,9] petechiae in the skin,[10] and vascular changes outside demyelinated areas.[11–13] No explanation has been given for the local factors causing damage in lesions, for their topography, or for their distribution in time.

The lack of a diagnostic test for MS, which can only be diagnosed with certainty at necropsy, must distort the epidemiological data used to support a viral aetiology. Prevalence rates are also unlikely to be accurate because one episode of neurological disturbance associated with demyelination[14] is by definition not MS and a patient may die of an unrelated disease before further symptoms develop and allow a diagnosis of MS. The not infrequent finding of occasional periventricular plaques at routine necropsy[15] supports this argument, but the use of the term multiple presupposes that more lesions must always occur.

In decompression sickness the areas of the nervous system most vulnerable to the localised hypoxia produced by small emboli are those with a high myelin content and a poor blood supply. Embolism has been discarded as a cause of MS, largely because most lesions do not resemble infarcts and usually surround small veins. Nevertheless, several embolic techniques produce perivenous demyelination.[16–18] In traumatic fat embolism perivascular haemorrhages, and occasionally demyelination, may be seen in the cerebral white matter;[19] but, because the onset of MS in most cases cannot be linked to an episode of trauma, the idea of MS being due to fat embolism has not been pursued. The possibility that conditions other than trauma may release depot fat into the systemic venous system, and the importance of the pulmonary filter, do not seem to have been considered. However, several recent neuropathological papers[13,20,21] which emphasise the vascular features of MS have opened the way for a reconsideration of embolic mechanisms.

VASCULAR FEATURES OF MULTIPLE SCLEROSIS

Rindfleisch, in 1863,[22] was the first to draw attention to the relation between MS lesions and the vessels of the nervous system, and most of the early writers stressed this feature. In those days patients often died in an acute phase of the disease and vascular relations were easier to determine. Ribbert[23] was the first to show that the lesions often extend along the vessels like a sleeve; the term plaque is thus misleading because it implies a two-dimensional structure. Dow and Berglund[11] suggested that a vessel may not be found in a lesion because of glial scarring. For this reason Scheinker[12] switched from studying old plaques to examining microscopic lesions and found that most of these small acutely demyelinated areas surrounded either a capillary, or, more usually, a small vein. The degree of axonal involvement ranged from practically nil to complete destruction; and it was most severe in the centre and progressively less so towards the margins of the plaque. Scheinker confirmed the occurrence of the perivascular haemorrhages first observed by Borst[24] and almost universally recorded by contemporary workers.

The vascular changes are not confined to demyelinated areas in the brain. Dow and Berglund[11] recorded dilatation and perivascular round-cell infiltration of the capillaries and veins outside plaques in up to 24% of their cases. Thrombosis, not a constant feature, was only found in vessels traversing lesions, but often proximal to, rather than wholly within, the demyelinated area. Scheinker[12] also found thrombi and commented on the difficulty in determining their location, because the demyelinated areas tend to extend into the surrounding nerve parenchyma, away from the primary blood vessel. He found that endothelial clots were common and that the greatest vessel damage was associated with the most severe lesions. Recent work[21] showing clearly the relation between the periventricular plaques and "terminal" veins supports the early work that stressed the perivascular nature of plaques, even when these were located under the pial surface or close to the cerebral ventricles.[25,26]

In the spinal cord the smaller wedge and oval shaped demyelinated areas often correspond to the territories of the transverse and perpendicular branches of the vasa corona arteries,[7] while the larger plaques, which may involve the white and grey matter equally, tend to be perivenular.[20,27]

No information is available on whether there is a relation between blood vessels and peripheral nerve lesions in MS, but there are many other indicators of vascular involvement. Periphlebitis of the retinal veins in MS tends to be fleeting,[8] but it may be associated with flame haemorrhages and may leave a residual sheathing of the veins.[9] Sheath formation is a result of long-standing obstruction to flow and of lipohyaline degeneration similar to that seen in the vessels in cerebral plaques.[7] The meningeal vessels in MS often show lymphocytic infiltration and may be surrounded by macrophages containing fat.[7] Biopsy specimens of skin petechiae in exacerbations of the disease show uncomplicated diapedesis of red cells.[10]

Studies of the blood-brain barrier provide further evidence of vascular disturbance in MS. Perfusion of the brain with trypan blue shows abnormal permeability of many of the vessels in MS lesions;[28] and computerised axial tomography with contrast enhancement show that these vessels are abnormally permeable in vivo.[29] The variations in permeability would seem to be consistent with the spectrum of damage seen in vessels microscopically.

The changes in vascular reactivity reported by Brickner[30] and Franklin[31] in MS patients include retinal arteriolar constriction, which is sometimes associated with the transient appearance of white streaks in the vessels, and obvious obstructions to flow. These are related to scotoma formation and a reduction in visual acuity which responds to vasodilating drugs. These workers also recorded brief attacks of other neurological disorders in MS patients and suggested that, because such attacks were so transient, they would often not be brought to the attention of neurologists.

EVIDENCE FOR EMBOLIC MECHANISM IN MULTIPLE SCLEROSIS

The sudden onset of neurological symptoms in the absence of a generalised illness is strong support for an embolic mechanism. The typical onset of MS is said to be the development, within a few hours or days, of the symptoms of a single focal lesion of the white matter.[32] Weakness of one or both lower limbs is the first symptom in about a third of cases and a disturbance of vision in almost another third. It may be argued that emboli are unlikely to be released singly; but not all emboli produce symptoms or signs. The great vascularity of most nervous tissue, especially the cerebral cortex, affords considerable protection against the effects of embolism, whereas areas with poor vascularity and little redundancy of function—for example, the long tracts of the spinal cord and the optic nerves, which contain large myelinated fibres—are more likely to give rise to symptoms. The distribution of plaques does correspond closely with the "watershed" areas of the cerebral circulation, particularly those between the anterior and middle cerebral arteries.[33] Similarly, in the spinal cord the watershed areas at the mid-cervical and lower thoracic levels are those most affected in both decompression sickness and MS.[34]

It is difficult to establish whether axons have been destroyed in plaques in the brain, but the symmetry and proximity of the two sides of the cord allows comparisons of fibre counts between damaged and undamaged areas. This elegant technique shows that there is consistenly a loss of at least 20% of axons in the demyelinated areas.[35] When plaques involve the ventral horns of the grey matter, neurone cell bodies may also be destroyed, and in some cases there is extensive central necrosis of the cord, fully consistent with embolic infarction.[7,34]

Surprisingly little experimental work has been undertaken in recent times into the effects of embolism on the central nervous system. In 1933 Putnam[16] reported that the intracarotid injection of cod-liver oil in the cat produced two types of lesion, both in the white matter—focal cystic infarcts and small perivenous areas of demyelination. He thought the appearances seemed more consistent with those of post-infectious encephalitis than with those of MS, but the lesions of MS are often perivenular. In-vivo studies in normal animals of fluorescein diffusing into the perivenular area show that the veins of the cerebral medulla are surrounded by capillary-free zones, which are thus dependent on diffusion from the veins for their nutrition.[36] Disappointment with the size of the lesions resulting from intra-arterial injection led Putnam[16] to conclude that embolism was not likely to be the cause of MS, but further work in which oils were injected upstream into the ligated longitudinal sinus in the dog produced larger lesions confined to the white matter and closely resembling those of MS.

Lumsden[37] firmly discounted the occurrence of micro-embolism in MS when his injections of cod-liver oil into the rat produced infarction and not demyelination. Of the 150 rats, 40% had no detectable lesions; most of the infarcts

produced were in the cerebral cortex, and only 21 (14%) had infarcts in the white matter. There are two serious criticisms of these experiments. Firstly, the carotid artery used for the injection was always ligated in order to control haemorrhage; and secondly, there was no attempt made to measure the size of or count the emboli.

Swank and Hain[17] injected different sizes of paraffin wax emboli into the carotid arteries of dogs. Paraffin wax was chosen because it was not sufficiently pliable to be moulded in transit and also because it was inert. Large numbers of emboli were introduced (one dog received 1250 million). Emboli of up to 60 μm diameter could pass from the cerebral arteries to the veins, despite the apparent absence of arteriovenous shunts. Some of the larger emboli produced infarction of the grey and white matter, but many of the smaller emboli were associated with venular damage and perivenous demyelination in the white matter in which many axons were preserved. Transient venous damage, said to result from the passage of emboli, also occurred, as shown by an increased permeability to trypan blue. Many of the wax emboli remained in the microcirculation for up to 4 months.

Similar experiments done in the investigation of acute fat embolism and with the use of plastic emboli of 30–37 μm diameter also showed that, although the emboli lodged in arterioles and capillaries, the damage produced was an increased transudation from the veins of the white matter[18]—the suggestion was that a fall in the oxygen tension of the cerebral venous blood after embolism probably caused endothelial damage. However, these experiments did not reproduce the petechial haemorrhages of human fat embolism. Even so, embolism can account for the topography of the lesions in the central nervous system, the frequent pathological changes in the vessels themselves, and their distribution in time. It also shows how lesions in the meninges, the peripheral nerves, the retina, and the skin can be linked with those in the brain and cord; it is difficult to see how else lesions in these sites may be linked.

Retrobulbar neuritis occurs not only in MS but also in other diseases—for example, syphilis,[38] where it is not disputed that the causative agent is blood-borne. The only part of the microcirculation of the nervous system which can be observed clinically is the retina, and the sporadic periphlebitis described in up to 23% of patients with MS[8] further supports an embolic mechanism. The lesions, which resemble those seen in acute fat embolism of the retina, may be fleeting, but severe cases tended to have obstruction to flow as shown by filling defects, haemorrhages, and the development of halo sheathing.[9] A film[39] of this sequence in a patient with terminal cancer showed that emboli arrested in the microcirculation and produced perivenous oedema and haemorrhage over a number of days along a considerable length of several veins. This remarkable film provides important evidence that embolic material can produce downstream venular damage in man. Such damage of the veins of the white matter is likely to be associated with cylindrical perivenous demyelination.

Although at the time the film was made it was thought that the emboli consisted of platelets, further study revealed features which strongly suggest that the embolic material was fat:

1. The material flowed along the arteries as a cylindrical plug suggesting that it was a liquid.
2. It was not miscible with blood.
3. The plug length in the arteries was up to fifteen times the diameter of the vessel and this increased up to about thirty times the diameter when the material flowed into the arterioles.
4. On reaching a bifurcation the embolus tended to split to produce two emboli with little reduction in velocity.
5. It was white.

Although the patient did not have pulmonary symptoms, this fat had almost certainly escaped from the lung.

EVIDENCE THAT DEPOT FAT IS THE SOURCE OF EMBOLI

Although pulmonary fat embolism is a well recognised sequel of all forms of trauma, it is not generally appreciated that fat is commonly found in the lungs at routine necropsy. Almost all diseases, poisonings, and injections to which the body has been subjected have been reported to be associated with fat embolism.[40] This association may account for the number of triggering factors implicated in MS.[41] The escape of pulmonary fat into the systemic circulation has been clearly recorded after acute trauma, and the resulting syndrome is associated with lesions in the brain, the cord, the meninges, the retina, and the skin.[34] The existence of an acute syndrome and the knowledge that fat emboli are commonly found in the lung raises the question of whether there can be a subacute form of the disease. It has not yet been recognised.

In traumatic fat embolism three types of cerebral lesions may occur—petechial haemorrhages, focal infarcts, and areas of myelin pallor[34]—and they occur almost exclusively in the white matter. Similar lesions have been described in the spinal cord,[42] although it is very unusual for the cord to be removed in cases of traumatic fat embolism.

The fact that lesions occur mainly in the cerebral white matter in acute fat embolism suggests that the emboli do not occlude the vessels of the cortex, but the globule count in the cortex may be ten times that in the white matter.[43] This paradox is central to this hypothesis explaining both the topography of lesions and their perivascular localisation. Courville[19] became aware of these features in the brain of a patient who died five days after the onset of acute fat embolism. Despite finding areas of myelin loss from axons bearing a "startling" resemblance to those seen in MS, he dismissed the possibility that depot fat embolism may be involved in MS—although he strongly supported Swank and Cullen's embolic theory based on plasma lipids.[44] Courville[19] knew that patients occasionally survive an episode of cerebral fat embolism, but there were then no reports of any necropsies that these patients might eventually have undergone. In 1970 McTaggart and Neubuerger[45] described the appearances of the brain of a patient who, after making a partial recovery from cerebral fat embolism, slowly deteriorated and died seven years later—there was extensive perivenous demyelination of the white matter, which in many areas showed relative preservation of axons, but there were no lesions in the cerebral cortex. Unfortunately, although the patient had initially been tetraplegic, the spinal cord was not examined.

It has also been suggested that the fat in traumatic fat embolism is derived from unstable plasma lipids,[46] because the intravenous injection into laboratory animals of a quantity of fat equal to their bone marrow volume does not cause death. However, soft tissue damage can release fat into the circulation and depot fat may be hydrolysed to produce free fatty acids. Peltier[47] has shown that some of the pulmonary lesions in fat embolism following trauma closely resemble the toxic damage produced by the injection of free fatty acids. The fat in the lungs and brain in acute fat embolism comes from depot sources because the emboli stain

brilliantly with fat stains (e.g., Scharlach R) and are doubly refractile in polarised light;[48] plasma lipids are stained by fat stains but are not doubly refractile. Watson,[49] after clinical and experimental studies, concluded that depot fat is the major, if not the only, source of embolic fat in acute fat embolism, the weight of evidence being against any significant contribution from plasma lipids.

If MS is associated with depot fat embolism then the migration of fat into the vessel wall and perivascular space found by Swank and Dugger[43] should allow its detection in the earliest lesions. In 1936 Greenfield and King[50] were puzzled by the presence of unusual lipids between nerve fibres in the early lesions in 13 patients; the concentration of globules, which were doubly refractile and stained brilliantly with Scharlach R, was greatest in the centre of the lesions and gradually reduced towards the periphery. They were thought to consist of fatty acids, possibly myelinated fibres which had inexplicably become transformed into simpler lipids. Greenfield and King could not explain how the transformation occurred—the process was different from anything ever described for secondary degeneration in the nervous system. The doubly refractile nature of the fats in MS lesions may not be unequivocal proof that they originate from depot fat, but their absence from early lesions would severely weaken a hypothesis linking MS with depot fat embolism. However, the products of myelin degradation will quickly mask the presence of depot fat in lesions.

Fat is a most unusual material. It can enter the systemic veins; escape from the pulmonary capillaries; cause vascular lesions in the nervous system, retina, meninges, and skin; produce venular damage in the brain; migrate into the vessel wall and perivascular space; release toxic breakdown products; and produce perivascular loss of myelin with axon preservation. The large number of fat emboli in the circulation in the acute fat embolism syndrome cause an arterial hypoxaemia,[51] with loss of consciousness, neurological damage, and petechiae. Occasional fat emboli are less likely to give rise to symptoms but the hypothesis is that they sometimes do, to cause MS; its pathogenesis according to this hypothesis is shown in fig. 1.

DISCUSSION

Although the severest lesions in MS resemble ischaemic infarcts, any theory of vascular causation must overcome the objection that most lesions do not look like infarcts.[6] Embolism is usually regarded as being synonymous with infarction, but fat embolism is an exception to this rule. Instead of obstructing arteries, depot fat emboli, being more liquid than other types of emboli, tend to progress into the microcirculation by elongating and dividing at points of bifurcation. The emboli may be arrested in the microcirculation or pass through into the veins and enter the lungs, where the low systolic pressure will favour their retention. Small emboli in the lung are silent and rarely cause infarction, presumably because of the great vascularity of the tissue and the high oxygen tensions present. These features also characterise the cerebral cortex, where the capillary density is about 1000 per square millimetre;[52] but capillaries in the white matter, where MS lesions are usually found, are longer and have fewer anastomoses, and their density is only about 300 per square millimetre. Although the animal experiments already discussed are able to account for the perivenous location of the lesions of MS, they have not accurately reproduced typical plaques in the white matter. This is not surprising since the animals used have much smaller brains than man (although erythrocyte and capillary dimensions vary little between mammalian species). So a lesion the size of a typical plaque in man would probably affect a considerable proportion of the total mass of a rat brain. Also, the shortness of the life expectancy in these animals does not give their plaques as much time as those in man have to develop or degenerate.

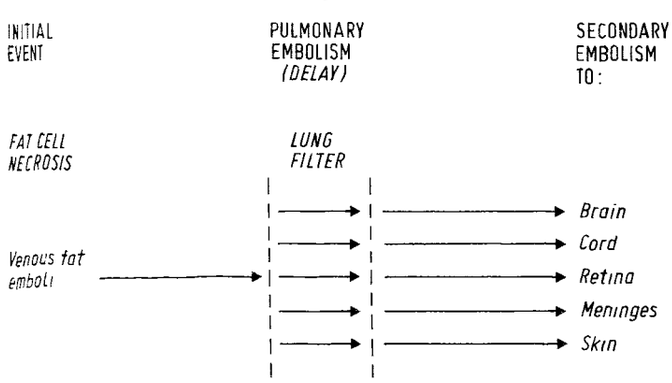

Fig. 1—Mechanism by which subacute fat embolism causes MS.

The patency of the veins in many plaques has been an argument against venous thrombosis being a cause of demyelination, but the knowledge that the occlusion may be temporary and proximal to the lesion explains why embolic fat has not been found even in very acute cases of MS. Such occlusion could produce symptoms not necessarily related to the site of eventual demyelination, and contrast-enhanced axial tomography has shown that in the acute phase of the disease there is often a discrepancy between the symptoms of the patient and the area of the blood-brain barrier that is damaged.[29] The fact that vascular damage and gliosis are commonly found outside plaques is strong evidence that they are primary events in MS and are not secondary to the release of any toxic products of demyelination or to an immunological attack on myelin. This argument is further strengthened by the finding[28] that although there are always some damaged vessels in plaques, others may be normal. These features are fully consistent with embolic damage.

Another argument to be overcome is the assertion that the axon is more vulnerable to hypoxia than the myelin sheath, although even in the generalised hypoxia of carbon monoxide poisoning demyelination occurs before damage to the axons.[16,37] Moreover, in an encephalopathy said to be due to hypertensive vascular disease[53] there are clearly defined areas of demyelination, which provide remarkable confirmation that vascular insufficiency can produce lesions similar to those seen in MS. The reason why axons may be spared in a very localised area of hypoxia, such as that produced by an embolus, is that those parts of the axon proximal and distal to the affected zone may provide nutritional support to the affected part by axial diffusion. Even so there is sometimes evidence of axonal and neuronal damage in MS lesions—for example, in plaques found in the cord some axons are always destroyed, and when the plaque affects the grey matter of the cord neurones may also be lost. The absence of axonal and neuronal damage, however, does not militate against an ischaemic cause for a lesion, because in experiments in which the cord was gradually compressed by a balloon catheter in the spinal canal the neurones in the grey matter were spared, but there was demyelination of axons.[54,55]

The third objection against vascular theories is that they cannot account for the recurrence of symptoms and the progression of lesions. The evidence from the film made of the retina[39] indicate that there are preferential pathways

taken by emboli, which greatly increase the chance of repeated embolism at a particular site. The demonstration, by axial tomography, of vascular leakage in vivo,[29] and the post-mortem demonstration of abnormal permeability in plaques,[28] indicate that the venular damage often persists. This long-term damage to the blood-brain barrier will clearly tend to cause the extension of lesions and progression of symptoms.

The implication of fat embolism as a cause of MS is certain to be seen as an attempt to link all cases of MS to trauma. A relation between the onset of the disease and trauma undoubtedly does exist in some patients, because a review of the literature has shown that in 5–15% of cases trauma precedes the onset of illness.[41] In a more recent report seven patients presented with MS soon after a traumatic episode.[15] However, a very wide range of other conditions could be the cause of the fat embolism. The role of the lung as a filter is crucial in preventing secondary embolism because if sufficiently large fat globules escape into the systemic arteries, then the nervous system is at special risk.

Not only is it clear that many conditions can be associated with minor pulmonary fat embolism, but it is also well established that time taken for fat to pass through the lung varies from hours to months. The delay between the occurrence of an event that releases emboli and the production of symptoms in the nervous system may, therefore, be so long that no connection between the two can be made. The short transit time seen in some patients with cerebral fat embolism also raises the possibility of embolic fat being occasionally responsible for spinal cord lesions following back injuries which are not associated with spinal fractures.[56]

The properties of depot fat may contribute to some features of the disease. Unlike the inert materials used experimentally, depot fat may be hydrolysed by endothelial lipases to release toxic free fatty acids,[47] and it may also contain cellular debris. The spectrum of fatty acids released depends on the composition of body fat which in turn is a reflection of the diet.[57] Free fatty acids are normally rapidly oxidised (they have a half-life of only 2 minutes in plasma[58]) but the hypoxia produced when an embolus reduces flow will slow their rate of destruction. By causing endothelial leakage, hypoxia may allow the diffusion of these and indeed any other substances present in blood into the interstitial fluid, where the glial boundaries may account for the complex patterns of demyelination seen in some cases.[34]

Fig. 2 illustrates a possible mechanism by which a demyelinating lesion is produced; it is based on Dow and Berglund's[11] reconstruction of the relationship between a thrombus and a downstream perivenous plaque from a case of MS when they made serial sections of the brain. The initial impaction of the embolus may cause pericapillary haemorrhage and thrombosis and provoke a glial reaction locally. When venous oxygen tension downstream in the white matter falls, endothelial leakage[18] will allow fatty acids produced by hydrolysis of the embolic fat to enter the interstitial fluid. As the myelin sheath undergoes progressive damage and some axons are gradually lost, a typical perivenular plaque develops.

The test of any theory of pathogenesis is whether it fits accurately with the pathological and clinical features of a disease. How fat embolism can account for the pathological and clinical features of MS is shown in tables I and II. However, although fat is the leading contender for the embolic material in most patients with MS, any circulating

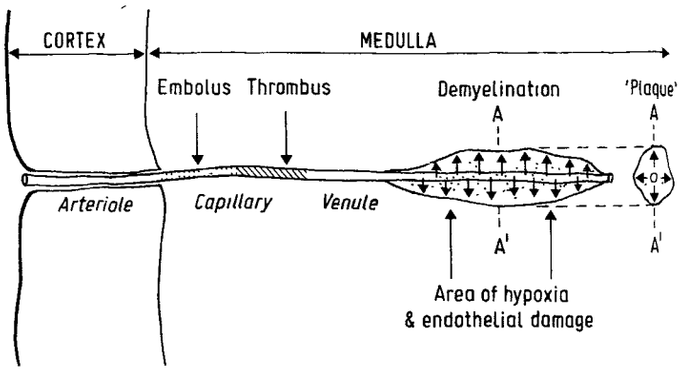

Fig. 2—Theoretical reconstruction of plaque formation in MS.

Based on data from Dow and Berglund.[11]

TABLE I—PATHOLOGICAL ASPECTS OF MULTIPLE SCLEROSIS CONSISTENT WITH DEPOT FAT EMBOLISM

Feature	Explanation
Topography of lesions[22,27,33]	Vascular
Pericapillary/venous localisation[11,12,13,23]	Fat emboli in the micro-circulation
Occasional perivascular haemorrhages[24]	Diapedesis of red cells due to endothelial damage
Typical cylindrical perivascular demyelination[23,11]	Endothelial damage. Hypoxic and toxic damage to myelin
Other patterns of demyelination[34]	Diffusion of fatty acids in the interstitial fluid
Extracellular fats in acute lesions[50]	Migration of embolic fat into the perivascular area[43]
Neurone cell body and axon destruction[6,34,35]	Hypoxic/toxic damage[47]
Progression of individual lesions[32]	Chronic leakage across the blood/brain barrier[28,29]
Endothelial clots and occasional thromboses[11,12]	Activation of clotting factors associated with emboli
Lipohyaline degeneration of vessels in C.N.S.[7] and retina[9]	Fatty infiltration of vessel walls[43]
Perivascular lesion in meninges,[7] retina[8,9] and skin[10]	Fat emboli in systemic vessels

TABLE II—CLINICAL FEATURES OF MULTIPLE SCLEROSIS CONSISTENT WITH DEPOT FAT EMBOLISM

Feature	Explanation
Proven associations, e.g., trauma,[15,41] vaccination[59] &c.	Release of fat into the circulation
Variable delay in the onset of neurological symptoms	Delayed release of fat emboli from the lung[51]
Sudden onset of neurological symptoms[32]	Arrest of emboli in cerebral/spinal cord vessels
Typical symptomatology i.e. visual, vestibular and cord[32,41]	Areas of poor vascularity in the brain and cord more prone to effects of emboli
Occasional localisation of symptoms to site of trauma[15]	Paradoxical vasoconstriction in nervous segments[60]
Variations in the severity of the disease[6]	Size, number, and toxicity of emboli, circulatory factors
Episodic nature of the acute symptoms[32]	Episodic nature of pulmonary and nervous system fat embolism
Recurrence of symptoms	Preferential routes for emboli; existing vascular damage
Raised serum lipases in attacks[61]	Release of endothelial lipases in lungs and nervous system[51]
Rarity in childhood[62] and usual post-pubertal onset[41]	Increase in lung size, increase and alteration in depot fat
Greater prevalence in females and cold latitudes	Amount of fat; cold-related vascular factors; medical detection; life expectancy[63]
Genetic factors	Pulmonary vascular size, ease of fat cell rupture
Dietary factors	Toxicity of fatty acids released by hydrolysis of depot fat[51,57]

agent escaping from the lung which arrests in the microcirculation of vulnerable areas of the nervous system could also cause perivascular demyelination.

ADDENDUM

Recognition of the importance of the vascular features in MS suggests a new approach to treatment. The response to steroids in acute cases may be due to their effect on vascular permeability, but hyperbaric oxygen, by paradoxically causing vasoconstriction yet increasing tissue oxygenation,[64] is a safer and better agent for treating hypoxia and cerebral oedema.[65] A patient who presented acutely (and whose clinical course was remarkably similar to that of one of Miller's cases[15]) has allowed this reasoning to be tested.

A 21-year-old man became briefly unconscious following a car accident and sustained a scalp laceration in the left parietal area. Two hours later he had a severe headache, momentary loss of vision in both eyes, and loss of sensation in the distribution of the left trigeminal nerve. Two weeks later he had slight swelling of the left optic disc associated with poor visual acuity and he complained of double vision, persistent headaches, and lassitude, although the facial numbness had resolved. No other neurological abnormality could be detected, but petechial haemorrhages, which had appeared on the anterior aspect of his thighs several days after the accident were still visible. The delayed (by 2 h) onset and clinical features are very compatible with subacute fat embolism, and so is the fact that the ophthalmic artery is a preferred pathway for emboli.[66] The efficacy of oxygen in fat embolism[51] and the proximity of a compression chamber suggested a trial of hyperbaric oxygen. The immediate improvement in visual acuity from 6/18 to 6/6 as pressure was increased to 2·8 bar confirmed the presence of hypoxia. Three sessions using a procedure from diving practice[67] continued the improvement and the patient reported that the double vision, which had prevented him from watching television, had gone and he felt generally much better. Over the past year his condition has remained stable, although he has had two very brief episodes of whole-body tingling, which may be due to the presence of small lesions in the posterior columns. It may be argued that this man did not have MS but, in view of the clinical features, what other diagnosis is possible?

Hyperbaric oxygen is an effective agent in the treatment of animals with experimental allergic encephalomyelitis (the experimental model for MS)[68,69] and a preliminary report of a favourable response in patients with established MS[70] has prompted a clinical trial. The relief of hypoxia by hyperbaric oxygen in acute MS should minimise the extent of the demyelination and neuronal damage and prevent the development of the progressive disease, whilst the stabilisation of the blood-brain barrier in chronic lesions may slow or even arrest further deterioration. Computerised tomography using contrast enhancement[29] will allow both these assertions to be tested in individual patients. Few therapeutic agents have the proven value and intrinsic safety of oxygen.

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Point of View

DRIFTING INTO PRIVATE HEALTH CARE

THE organisation of health care in Britain is coming to resemble that in the United States, though the present National Health Service is probably too popular for a complete shift to occur. Firstly, there has been an increase in privately owned hospital beds and in the involvement of private contractors in N.H.S. support services, such as hospital cleaning. The Government, though not the originator, has encouraged these changes as well as joint use of diagnostic facilities. Secondly, doctors are increasing the proportion of their earnings from private sources, especially since the revision of the consultant contract. Thirdly, there is movement towards the funding of health services on insurance principles, manifested both by the growth of provident association coverage, the provision of income tax relief on premiums, and general interest in movement towards some unspecified form of insurance funding for the N.H.S. All this suggests that there is something to be learned from American experience.

The striking point of comparison is that the different structures of health services in the two countries produce remarkably similar outcomes in terms of rates and causes of death, morbidity and disability, and difficulties in the operation of health services. Amongst the difficulties, though in different degrees, are rapidly rising unit costs of medical treatment, emphasis on acute medicine in the face of an increasingly elderly population, incentives for the overuse of hospitals, and the increasing use of resources on intensive diagnosis and treatment, with the result in the U.S.A. that cost per patient rises while in Britain less patients are treated. Other shared problems include more occupational fragmentation, more health workers employed, gross class and geographical inequalities in the distribution of health-care resources, and increasing pressure-group activity and litigation by consumers.

It is the common factor of the power of health-service providers which maintains these similarities in the face of very different systems of organisation. But there is one crucial contrast between the countries. Britain spends about 6% of gross national product on health care, the U.S.A. almost 10%. Britain's emphasis is on controlling the total sum, leaving service providers relatively unconstrained by policy on how this is used. No such control has been possible in the U.S.A., with the result that total spending has risen rapidly. However, there has been much more concern with piecemeal forms of control over quality of care, capital developments, and insurance reimbursements, as well as with health maintenance organisations, which transfer the risk of expensive care to the doctor.

It is likely that increasing privatisation of health care in Britain will lead to an increase in total expenditure which will, at best, be a mixed blessing for both consumers and providers of health care. Firstly, much of the cost will be met by employers as health insurance is demanded as a condition of employment. Secondly, insurance organisations and private hospital proprietors will begin to make inroads into clinical freedom in order to ensure price and quality competitiveness; some doctors may not regard an increase in medical incomes as being sufficient compensation. Thirdly, administration costs will rise as a proportion of the total because of duplication and the much higher marginal costs of raising revenue by insurance rather than taxation. Fourthly, the geographical and class distribution of health-care expenditure, staff, and facilities will become more unequal than at present as premiums for the non-employed rise and the public health service becomes inferior.

Nor is it likely that this will improve the health status of even those sections of the population who utilise the private sector. Changes of this order will be almost impossible to reverse since they will create new vested interests. To encourage the private sector cannot, therefore, be seen as an "experiment" but as a self-fulfilling prophecy which will thwart any aspirations to a public health policy.

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