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# Bacterial toxins and Multiple Sclerosis

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**Abstract**

The primary pathogenetic mechanism responsible for the distinctive demyelinating lesions in the Central Nervous System (CNS) in Multiple Sclerosis (MS), first described in remarkable detail by Charcot more than 170 years ago, remains one of the most baffling conundrums in medicine. A possible role for bacterial cell molecules and transportable proteins in the pathogenesis of MS is reviewed. The ability of bacterial toxins to distort immunity and to cause distinctive toxic damage in the nervous system is discussed in the light of largely forgotten data linking bacterial nasopharyngeal infections with optic neuritis, optochiasmatic arachnoiditis and MS. While the blood–brain barrier substantially protects the CNS from hematogenous toxins, there is a route by which the barrier may be by-passed. Data is reviewed which shows that the CSF and extra-cellular fluid circulation is bi-directionally linked to the lymphatic drainage channels of the nasopharyngeal mucosa. While this provides a facility by which the CNS may mount immunological responses to antigenic challenges from within, it is also a route by which products of nasopharyngeal infection may drain into the CNS and be processed by the immune cells of the meninges and Virchow–Robin perivascular spaces. If potentially toxic bacterial products are identified in early MS tissues at these sites, this would provide an entirely new insight into the pathogenetic mechanisms of this frustratingly enigmatic disease.


*Keywords:* Multiple Sclerosis; Paranasal infections; Bacterial transportable toxins; Mucosal lymphatics; Cerebrospinal fluid

> 'There is a true missing link in our understanding of MS and we must be open to surprises' Bruce Trapp. Ann Neurol 2004.

## 1. Introduction

The celebrated clinical and histopathological accounts of 'La sclerose en plaques disseminées' by Jean-Martin Charcot and his colleagues over the final three decades of the nineteenth century [1] signalled the beginnings of modern investigative medicine. The accurate clinical description of the symptoms and signs of Multiple Sclerosis (MS), combined with the discovery of the tissue changes that accounted for them, produced for the first time a clear clinico-pathological definition of a disease. Medical researchers grasped with enthusiasm the new and potent opportunities of recognising, naming and getting to know the diseases they were attempting to cure.

It is remarkable that after almost 170 years of intense, and in recent times, technologically powerful investigations, the cause and cure of MS seem to be as elusive as ever. The isolated patches of inflammation and demyelination scattered throughout the central nervous system (CNS) and optic nerves, usefully define the disease but their cause remains a mystery. The hypothesis of an autoimmune T-cell mediated mechanism of demyelination in MS – the 'prototype autoimmune disease of the CNS'[2] – has come to be repeated so many times, that it has all but acquired for most researchers, clinicians and authors of neurological texts, the status of fact. It has also become the 'coherent and focussed foundation' of all main line modern therapies [2]. Acknowledgement of the need for an environmental trigger in MS [3] has directed the search for microbial agents that might induce by some sort of molecular mimicry an autoimmune response to myelin antigens. The search, extending for over 50 years has been heavily biased towards viruses. Virus infection and latency have been perceived to have unique and particularly promising mechanisms of tissue damage, especially in relation to enigmatic diseases [4]. The search for a viral etiology of MS continues [5]. The possibility

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that a virus may yet be uncovered in the CNS has recently received indirect support from an analysis of IgG genes in MS which point to a conventional antigen-driven antibody response [6]. While it is still credible that a neurotropic viral agent could have evaded discovery, it is not at all likely that a bacterium could have done so in a similar way. Failure to confirm reports of the presence of *Chlamydia pneumoniae* in the CNS of MS cases [7] was not unexpected. The likelihood of detection of bacterial cells in MS tissues by experienced histopathologists, and the characteristics of the cellular responses in MS, seem to weigh heavily against any direct role for bacteria, including obligate intracellular organisms.

Despite the relative neglect of bacterial infection in MS research, studies of the role of bacterial antigens in autoimmunity and in aberrant immune responses have been of special interest to immunologists [8]. The potential of bacterial antigens to mimic human tissues is considerably greater than that of viruses. The number and variety of bacterial species available, especially within the normal flora, greatly exceeds that of viruses. While individual viruses have between 3 and 50 kb of genomic nucleic acid coding for up to 50 polypeptides; bacterial cells have up to 5000 kb of DNA coding for approximately 5000 polypeptides [9].

Many bacterial species produce 'exogenous superantigens', a heterogeneous selection of cellular and transportable molecules with the ability to non-specifically activate lymphocytes. Staphylococcal enterotoxins, the most potent and most intensively studied of these molecules, bind simultaneously to the T-cell receptor Vβ domain, and to the α chain of the Class II MHC molecule. This results in an activation signal inducing T-cell proliferation irrespective of any previously acquired antigenic specificity. Similarly, exogenous superantigen derived from mycoplasma bridges the CD4+T-cell–B-cell interaction to induce B-cell clonal proliferation and autoantibody [10]. The ability of bacterial superantigens to stimulate autoimmunity has been demonstrated by inducing exacerbations of experimental allergic encephalomyelitis (EAE) in myelin sensitized animals [11]. A similar activation has been demonstrated *in vitro* using autoreactive T-cells from patients with MS [12]. A possible association of Staphylococcal antigens with MS has been investigated by Aasjord and colleagues [13] on account of the ability of these antigens to induce EAE in rabbits. Tantalising data relating to a possible role for extrinsic superantigen in MS has come from studies of the T-cell receptor (TCR) repertoire in identical twins discordant for MS. The discordant monozygotic twin appears to use different TCRs in response to both self (myelin basic protein) and foreign extrinsic antigens (tetanus toxoid). This could account for the non-genetic element in discordance and could be effected by exposure of the MS twin to extrinsic superantigen [14,15].

Bacterial heat shock proteins (HSPs) provide another potential mechanism of autoimmunity in tissues exposed to bacterial molecules. These highly conserved immunodominant antigens which are upregulated by both host and pathogen during the course of infection, have typically more than 50% amino acid identity between bacteria and human tissues. The possible involvement of HSPs in MS has been reviewed by Ransohoff and Ruddick [16].

A significant step beyond these speculations is the evidence linking certain subtypes of the Guillain–Barré syndrome (GBS) with antibodies to lipo-oligosaccharide induced by infection with *Campylobacter jejuni* [17]. Clinical and epidemiological data had already linked GBS with *Campylobacter* infection. The evidence for a specific pathogenic mechanism involving complement fixing anti-myelin, cross-reacting antibodies in these peripheral neuropathies has been strongly supported by the observation of co-locating IgM-C3d immune complexes on the intact myelin sheath [18]. These localizing immunocytological observations have set a useful precedent for any subsequent claimants when an antibody mediated primary mechanism of demyelination is proposed.

This current interest in bacterial products as candidate antigens or co-factors in the etiology of MS is based on the assumption that demyelination is dependent on an inflammatory 'autoimmune' mechanism. Of the bacterial products that are known to damage the cells and tissues of the nervous system the great majority are specific toxins and enzymes that act directly on specific tissue targets [19].

## 2. Primary pathogenic mechanisms in MS. Inflammatory or toxi-degenerative?

The primacy of inflammation in MS is once again being questioned and vigorously debated [20,21]. While there has been an undercurrent of clinical suspicion that the severity of an attack and the subsequent progression of disability do not necessarily correlate with CNS lesion activity, magnetic resonance imaging data now points to a dissociation between inflammatory activity of lesions and the clinical outcome [22]. Various anti-inflammatory therapies have been shown to reduce inflammation, but their effect on the progress of disability is much less certain [23,24]. The observations of early axonal degeneration in active MS plaques [25] and in normal appearing white matter [26,27] has raised the question of an initial toxi-degenerative process with an important bearing on long term disability. A more pertinent line of evidence relating to primary events are the recent reports describing the characteristics of 'pre-demyelinating' lesions in normal appearing tissues obtained at autopsy from unusually early cases [28,29]. Primordial events anticipating the development of focal demyelination are characterised by microglial cell activation and the presence of membrane bound C3d–IgG immune complexes in sub-ependymal, sub-pial and perivascular parenchyma [29]. These lesions evidently precede blood–brain barrier disruption as they do not show either leakage of plasma proteins or CD4+T-cell infiltration. The surfaces of myelinated axons may show the modest beginnings of myelin lysis, but myelin sheaths, in significant contrast to the peripheral neuropathies [18], are not apparently opsonized at this stage, by complement or immunoglobulin, despite the presence of C3d–IgG complexes. Furthermore,

oligodendrocytes are significantly depleted in these lesions and may be undergoing apoptosis [28]. These observations probably relate to earlier reports of astrocyte activation [30] and Virchow–Robin perivascular cuffing [31] in otherwise normal CNS tissues. They have been supported by data from magnetic resonance diffusion imaging and spectroscopy, which points to a 'subtle progressive myelinolysis' in normal appearing brain [32,33]. Taken together these observations suggest the presence of a myelinolytic complement fixing antigen, toxic for oligodendrocytes and axons, and infiltrating the CNS parenchyma *via* the extracellular fluid circulation and CSF [29].

## 3. Bacterial exotoxins and demyelination

The observations of many of the early neuropathologists [34,35] led them to favor a primary toxi-degenerative mechanism of demyelination which was then followed by secondary inflammation. It was not at all clear how putative hematogenous toxins could gain access to the CNS. Dawson's observations [35] led him to postulate that a microbial toxin intermittently disseminated in the CSF and extracellular fluids of the CNS was responsible for periventricular and perivascular demyelination. The idea of the involvement of a microbial toxin or myelinolytic enzyme had been suggested both by the histology of demyelination and by the behaviour and location of plaques. Clearly, once initiated, myelin lysis could proceed along a number of different pathways. However, by employing a miscellany of special myelin and tissue stains, now rarely used, these histologists had observed in early acute MS plaques, the 'erosion and lysis of the sheath from outside' [36] producing free myelin debris. This crucial observation, later supported by electron microscopy [37], suggested a primary myelinolytic factor. This contrasted with the degenerative decay from within the sheath observed for example in the leukodystrophies and in Wallerian degeneration [38]. Secondly, the early pathologists emphasised that acute lesions show relatively little leukocytic infiltration [36], an observation which, as we have seen, has been recently confirmed in 'pre-demyelinating' lesions [28,29]. This also pointed to the activity of a toxi-degenerative process as an antecedent to inflammation. Thirdly, the spreading of the plaque leading edge, in all directions regardless of tissue boundaries, most dramatically seen in, but by no means confined to the 'Balo' variety of MS, speaks of the spread by diffusion of the putative lytic factor. Finally, the observation that plaques most frequently develop from surfaces bathed in CSF, suggested the dissemination of a myelinolytic agent *via* the extracellular fluid circulation of the CNS. The recent reports of the frequency of sub-pial cortical demyelination in MS [39] reinforces this picture.

These observations were followed by animal experiments to demonstrate the ability of various bacterial toxins and lipolytic hemolysins to reproduce plaque-like lesions and attempts to demonstrate toxic or lytic substances in CSF or serum [36]. These experiments were to be confounded by the observation that many endogenous lytic enzymes are activated in plaques and usually occur in other inflammatory and degenerative conditions [40]. There was no method available to differentiate intrinsic lytic molecules generated as a secondary tissue response, from putative primary extrinsic microbial toxins.

## 4. Access of toxins to the CNS: Is MS an 'unrecognised rhinopathy'?

Dawson's dilemma in proposing a primary role for an extrinsic microbial toxin was to determine how significant quantities of toxin, presumed to be hematogenous, could gain access to the CNS without a serious and obvious breach in the blood–brain barrier [35]. He concurred with the proposition of colleagues that such toxins were likely to arise from foci located outside the CNS, as 'Loci minoris resistentiae', but a route of access into the extracellular fluid circulation of the CNS was not immediately obvious. It seems that he was not aware of the body of published clinical data linking optic nerve demyelination with foci of nasopharyngeal inflammation, and in particular, inflammatory disease of the posterior nasal sinuses.

Tadhkirat al-kahhalin (the oculist's memorandum) is believed to be the oldest complete original text extant in Arabic devoted to the anatomy, pathology and treatment of the eye. The author 'Ali ibn Issa', a contemporary of Omar Khayyam of Naishapur, was the best known oculist of the Arab world and practized in Baghdad during the first half of the eleventh century. In the late fifteenth century, Tadhkirat al-kahhalin was translated into Hebrew and twice into Latin as 'Tractus de oculis Jesu ben Hali'. A German translation in 1904 is contained in 'Die arabischen Augenarte nach den Quellen' [41]. In a section dealing with visual disturbances with no immediately obvious cause Ali ibn Issa describes a rapidly developing 'darkness of the eye' accompanied by deep orbital pain. He interprets these symptoms as being due to 'compression, congestion and inflammation' and states that in his experience, the condition is associated with the accumulation of 'catarrh' which has penetrated the optic nerve.

The idea that the optic nerve might be especially vulnerable to the extension of inflammation arising from disease of the paranasal sinuses was based on what was known about the anatomy of the region and in particular the intimate proximity of the nerve and its meninges to ethmoidal and sphenoidal air cells. The sinus mucosa may lie on optic nerve dura without the protection of intervening bone. It was also well known to early medical practitioners (and, one hopes, even to modern medical students) that frank sepsis is particularly liable to extend into the brain from nasal and facial lesions.

Reports claiming that optic neuritis was a complication of inflammatory disease of the nasal sinuses appear in the medical literature of the 18th and early 19th centuries. Beer's article in 1817 'On vicarious blindness from suppressed snuffles without evident accumulation of mucus in the frontal

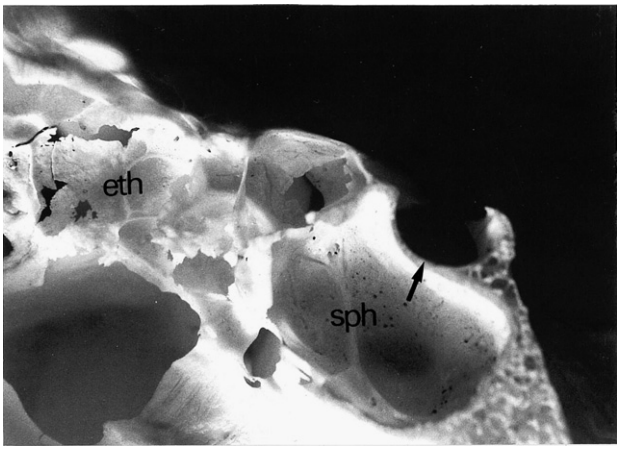


Fig. 1. Median sagittal section through the sella turcica (arrow) showing deeply penetrating sphenoidal (sph) and ethmoidal (eth) cells, with paper thin walls. Onodi collection. Royal College of Surgeons of England.

sinus' quoted by White [42], was followed by a steady stream of similar case reports. The comprehensive review by Crane [43] in 1927 gives a good picture of the ferment of interest that had now developed among practising ophthalmologists and oto-rhino-laryngologists. It was of course well documented that infection from pyogenic spheno-ethmoiditis risked extension into the optic canal and orbit by the necrotic erosion of bone or by a retrograde venous thrombosis into contiguous structures, but the emphasis of most of these early reports was that optic nerve inflammation was unexpectedly associated with a less florid and certainly more limited inflammation which could lack any of the usual signs or symptoms of a pyogenic infection. Remarking on this recurring theme in the literature, Baratoux [44] in 1923 and Canuyt et al. [45] in 1925 suggested that in all cases of optic neuritis sinus infection may be implicated and that the posterior air cells should be carefully examined to exclude peri-optic inflammation.

By the end of the 1920s a large literature on optic neuritis in relation to sinus disease, usefully reviewed by Thompson in 1929 [46], had appeared in Europe and in the USA. It was now confidently claimed that the majority of cases of optic neuritis had their origin in an 'unrecognised rhinopathy' [47] and therefore warranted urgent surgical exploration. This movement into surgical intervention prompted Herzog [48] and others to remind over-enthusiastic oto-rhino-laryngologists that 'rhinogenic' optic neuritis was likely to be of minor importance compared with that variety of the condition which is so often associated with MS. However, Herzog [48] had found some evidence of sinus inflammation in no fewer than 16 of 28 cases of optic neuritis. In a survey of 500 patients with clinical evidence of sinusitis, examined over a period of 8 years at his Innsbruck clinic, the very high incidence of visual field defects pointed to a causal link between optic nerve damage and sinusitis. McMahon [49] in 1926 reported a similar study of 70 patients with histologically confirmed spheno-ethmoiditis over a period of 18 months and found evidence of optic neuritis in 5, an unexpectedly high rate in a European population. The criteria by which a diagnosis of 'optic neuritis' was made in these studies were not always clear, but in spite of this problem it seemed likely that optic nerve damage and posterior sinus infections were in some way linked. Herzog [48] had also pointed out that the histological changes in sinus tissues removed from patients with optic neuritis seemed too slight to account for demyelinating damage to the optic nerve. When he studied the normal histology of the region in 12 cadavers he found a considerable variation in the structure and density of the bone forming the wall of the optic canal and the contiguous sphenoidal and ethmoidal air cells. The bone could be compact but in some cases cortical spaces abounded and offered 'uninterrupted communication' between the sinus sub-mucosa and the optic nerve dura. Reviewing tissues removed as blocks from patients with a history of optic neuritis he found that even when the mucosal epithelium appeared normal the sub-mucosa showed chronic inflammatory degeneration which had extended into the cortical spaces of cancellous bone producing a 'productive osteitis'.

These histopathological observations confirmed by McMahon [49] were later extended in 1927 by Sluder [50] and Oliver and Crowe [51]. The histology showed what many clinicians had suspected, namely the existence of a chronic locally destructive and frequently sub-clinical sub-mucosal disease which could extend into deeper structures. It was speculated that the structure of the bony wall of the air cell might be the key factor determining the outcome of such mucosal inflammation. In addition, the lymphatic channels between the posterior sinuses and the posterior orbital structures provided what Crane [43] had described as 'a network of communication' by which bacterial toxins and products of inflammation could spread through the region.

The anatomical researches of Onodi [52] (1908), Loeb [53] (1909), Schaeffer [54] (1920) and Van Alyea [55] (1941), showed that during the second decade of life the sphenoidal sinuses and some ethmoidal cells actively

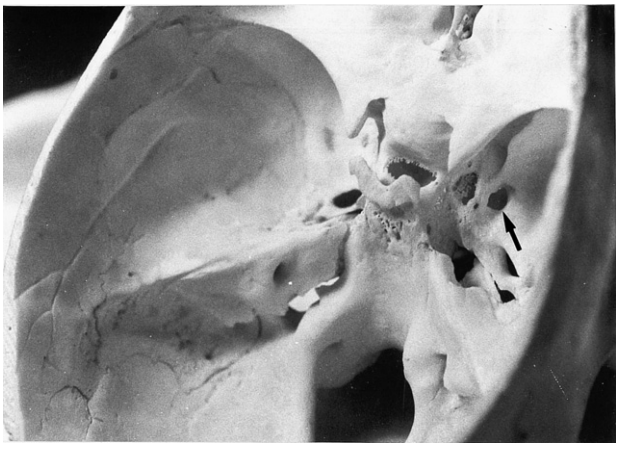

Fig. 2. Multiple defects in the anterior floor of the middle cranial fossa. A large defect (arrow) is present in the wall of a posterior ethmoidal cell. Skull collection at Clare College, Cambridge. Courtesy of Dr Gordon Wright.

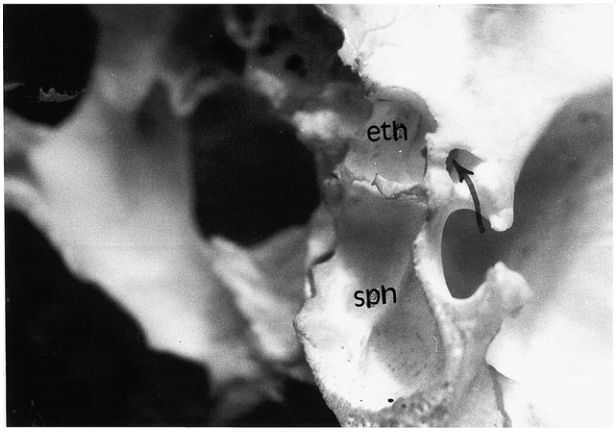


Fig. 3. Localised defect in the wall of the optic canal (arrow), communicating with a spheno-ethmoidal sinus. Onodi collection. Royal College of Surgeons of England.

excavate the body and wings of the sphenoid bone producing highly variable and irregular blindly-ending recesses, deeply penetrating the bony structures of the floor of the middle cranial fossa (Fig. 1). The drainage of these cells is poor, making them particularly susceptible to chronic infection. A second consequence of posterior sinus cell development is that the meninges of the optic nerves, the sub-arachnoid cisterns and the ventricular system may be separated from these recesses by the thinnest layer of bone (Fig. 1). In some instances the sinus mucosa herniates through bony defects and comes to lie directly on dura. Examples of these 'defects' are to be found in skull collections in the medical schools (Fig. 2). The 'Onodi collection' of skulls and sphenoid blocks held at the Royal College of Surgeons of England, a substantial part of which was lost to bomb damage during the London blitz, formally demonstrates these defects and the great variations in the anatomy of the region (Figs. 1 and 3). Onodi's thesis was that because of the anatomy, the posterior sinuses have both a special predisposition to chronic infection, and a potentially defective barrier to the extension of infection and inflammation to the contiguous structures of the brain, including the ventricular and sub-arachnoid fluid circulation.

In 1931 Vail [56] reported 15 cases of optic neuritis in which X-rays and surgical exploration appeared to implicate posterior sinus infection as the likely cause. He also observed that optic neuritis and sinusitis were more frequent in the colder months of the year and that patients with optic neuritis would commonly relate the attack to a preceding coryza or 'flu'. McMahon's clinical and histopathological study [49] had established hyperplastic submucosal inflammation with osteitis as a definite clinical entity. He proceeded to show that this condition was twice as common in females as in males, and that the incidence steeply rose in the third decade of life, reached a peak around 30 years, and gradually declined in the fourth and fifth decades. It was evident that chronic spheno-ethmoiditis and optic neuritis, shared distinctive epidemiological characteristics. It did not escape Vail's notice that they were also shared with MS. Did the 'virus' that caused MS, he wondered, access the CNS *via* the posterior sinuses, and should diseased sinuses be treated when they were discovered in patients with MS?

Derrick Vail [57], Harris Vail's father, now called attention to the possible significance of the foci of chronic meningeal inflammation and fibrosis which had been described around the optic nerves and chiasm in posterior sinusitis, in optic neuritis and also in MS. The condition known as 'optochiasmatic arachnoiditis' had first been reported by Balado and Satanowski [58] in 1929 in young adults with unilateral or bilateral visual loss, and has been more recently associated with MS by Bell et al. [59] in 1975. Vail now suggested that the posterior sinuses might be the 'portal of entry' of a bacterial toxin or virus so that optic neuritis, MS and optochiasmatic arachnoiditis 'might be part of the same pathological process'.

It seems that Derrick Vail had not seen Dawson's celebrated *magnum opus*[35] 'The Histology of Disseminated Sclerosis' appropriately described as 'the greatest pathological account of MS in the English language' [1]. Dawson, as we have seen, had developed his hypothesis of the dissemination of bacterial toxin throughout the extracellular fluid compartments of the CNS. He also described isolated foci of meningeal inflammation and fibrosis, as being 'of great importance in relation to the pathogenesis' of MS.

If Dawson had been aware of the direct route for the access of bacterial products into the CNS proposed by Vail [56] and his otorhinological predecessors, he would doubtless have found the work of Orr and Rose [60] even more intriguing and relevant than he already believed it to be. Orr and Rose were experimental neuropathologists working in the north of England and publishing extensively between 1903 and 1914. Although references to their work have long since disappeared from the literature, both Dawson [35] and Lumsden [36] recognised its neuropathological relevance. In a series of experiments [60], sealed semipermeable capsules containing bacterial cultures were implanted in tissues alongside spinal and cranial nerve trunks in rabbits. Bacterial transportable toxins and enzymes diffusing into the perineural tissues were taken up by the perineural lymphatics, inducing a limited lymphocytic and plasma cell response. The bacterial products were transported centrally in the neural sheaths without evidence of nerve involvement until, arriving in spinal or cerebral tissue, microglial activation and demyelination were induced in the neuropil. There was no knowledge of the nature of the transportables produced by the encapsulated cultures at the time, but the use of *Staphylococcus aureus* would have produced both α and β-haemolysins [61]. We now know that Staphylococcal α haemolysin is a channel forming membrane toxin causing lethal small ion leakage from target cells [62], and that β toxin is a sphingomyelinase, lytic for myelin containing membranes [63].

These insights were lost in the ensuing storm of controversy that was now developing. The beneficial and sometimes dramatic results of surgical exploration and drainage of the

posterior sinuses in patients with optic neuritis were taken by the 'interventionists' as 'definite proof' that infected sinuses caused optic neuritis and in some cases, MS. Surgeons were now under pressure to operate even when objective evidence of sinus disease was wanting. Brunner [64], speaking for the critics of surgical intervention in 1941, correctly pointed out that many cases of optic neuritis recovered spontaneously if left alone and vision could return to normal. The interventionists he warned had fallen into the trap of employing 'the physician's friend', the statistical phenomenon we now recognise as regression to the mean, where the intervention takes place at the height of the exacerbation, and the 'beneficial response' is no more than the inevitable improvement characteristic of the disease. The technique of the controlled trial had not yet been developed and in the event no trial designed to settle the matter was ever undertaken. At the same time it was found that, when cases of optic neuritis were followed up over many years, up to 75% [65] turned out to be MS. Thus it was concluded in influential clinical circles that since most optic neuritis was 'caused' by MS it could not therefore be caused by sinusitis. This implied that, whatever the cause of MS might be, sinusitis had been excluded as a possible cause. The *non sequitur* was entirely overlooked. In the event the total and fastidious rejection of surgical intervention in the treatment of optic neuritis precluded any imaginative enquiry into the pathogenesis of optic nerve damage at this uniquely vulnerable site.

By the end of the Second World War virtually nothing remained of this period of intense interest and activity. References in clinical and pathological texts died out, and research into the cause of MS and optic neuritis became increasingly dominated by the new immunology. EAE was enthusiastically embraced and ingeniously tailored in every way possible to resemble MS. EAE continues to be experimentally adapted [66] to model the presumed autoimmune mechanism of demyelination in MS, despite the failure to demonstrate a target autoantigen in the CNS [21].

Sporadic reports linking optic neuritis with sinusitis continued to appear in the literature, (Tarkanen and Tarkanen [67], 1971, Awerbuch, Labadie and Van Dalen [68], 1989, Rothstein et al. [69]) but without any experimental evidence that might shed light on the clinical association. Was this a rare but intriguing curiosity or an important clue to the etiology of optic neuritis and possibly MS? An epidemiological study by Gay et al. in 1986 [70] showing highly significant links between clinically diagnosed sinusitis and the development of MS, using family practice data, was rapidly confirmed by Callaghan [71]. Both studies confirmed that MS and sinus infections were significantly associated in frequency, severity, age of attack, season of attack and in the timing of attacks. Both diseases affected females more frequently than males in a ratio of 2:1 and at a slightly earlier age. The association of paranasal sinus radiological abnormalities and optic neuritis, which Bradley and Whitty [72] had noted in 1967, was not detected in a small retrospective study of MS patients by Martyn [73].

## 5. CNS fluid drainage and the lymphatic system: Current concepts

Vail [56], unaware of Dawson's thinking [35], suggested that bacterial toxins might diffuse into the CNS *via* lesions in the paranasal sinuses. The intimate anatomical relations of the posterior nasal sinus mucosa to the optic nerve sheath had suggested to some that vascular and lymphatic channels linking the drainage of the sinus mucosa with CSF might be a route by which bacteria, bacterial enzymes or toxins could gain direct access to the CNS in significant but limited quantities.

Drainage of CSF into the blood takes place *via* the arachnoid villi, and a system of lymphatic vessels does not occur in the CNS. However, tracers introduced into CSF rapidly appear in the nasal mucosa *via* the perineural sheaths of the olfactory nerves as they pass through the cribriform plate [74]. In addition, Foldi [75] has drawn attention to the role of perineural and perivascular channels in connecting the drainage of CSF and of CNS extracellular fluid, with the lymphatic system of the head and neck. Tracers, both soluble and particulate, injected into CSF reach the cervical lymphatics by way of the leptomeningeal sheaths running with cranial and spinal nerves and in the walls of cerebral arteries. Tracers introduced into CSF appear in epidural loose tissue and in the nasal mucosa where they are picked up by the normal lymphatic channels of these sites. The neuropathological and immunological implications of these communications between nasal structures and the CSF have been reviewed by Esiri and Gay [76]. When microbial antigens are released into posterior sinus submucosa and contiguous tissues either they may be processed by the lymphatics of the head and neck, or they may enter the CSF and extra cellular fluid compartment of the CNS and be processed by the macrophages of the pia-arachnoid and perivascular spaces. Such an incorporation of the lymphatic drainage of the nasopharynx into the drainage of the CNS is intimated by Prineas' observations [77] that the distribution and organisation of inflammatory cells in chronic active MS tissues closely resembles the antibody processing medullary region of lymph nodes.

## 6. Conclusions

There is evidence to suggest that posterior sinus submucosal infection may be linked to the development of both optic neuritis and MS. The recent evidence pointing to a primary toxi-degenerative pathogenesis of MS suggests that the ideas of Bruce and Dawson [78], later developed by Dawson [35], that primary damage in MS could be attributable to the intermittent dissemination of a bacterial toxin *via* the CSF, should be reconsidered and investigated. The recent demonstration of immune complexes distributed throughout the extracellular fluid compartments of the CNS in very early cases [29], and the demonstration of meningeal B-cell follicles with germinal centres [79], points to the presence of an extrinsic complement fixing antigen. Further

analysis of these complexes [80] would seem to offer an opportunity of identifying the nature of the primary insult in MS, and the missing link in our understanding of this enigmatic disease.

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