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Futility of the autoimmune orthodoxy in multiple sclerosis research

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"Experimental allergic encephalomyelitis is … a true autoimmune disorder. It has been accepted as an animal model of multiple sclerosis … However, a false orthodoxy claiming that multiple sclerosis is an autoimmune disorder has developed and formed the present basis of treatment, drug trials and research. The outcome of this misplaced creed has been truly catastrophic."

Multiple sclerosis (MS) is a chronic disease of unknown etiology that primarily affects the human CNS. While its pathology has been well described, its pathogenesis is still unknown. Multiple epidemiological studies carried out in Europe, the USA and Canada have highlighted the difficulty in its study because of the many complex combinatory roles of genetic factors, diagnostic variability and its often long asymptomatic clinical course. In addition, there is no specific diagnostic test. All this may explain the great variability in the methodology of the multiple therapeutic trials for this disorder [1,2].

MS, acute disseminated encephalomyelitis & experimental allergic encephalomyelitis

The enigma of this curious disease can be demonstrated by the occurrence of MS being greater in first-, second- and third-degree relatives, while its definite polygenic etiology still defies elucidation. The disease bears some clinical resemblance to acute disseminated encephalomyelitis (ADEM), a disorder that may occur spontaneously, or after a viral infection or different immunizations, including rabies [3]. Their tentative similarity suggests that MS could be an immunological disorder, an idea that gained support from those accepting experimental allergic encephalomyelitis (EAE) as the putative animal model for MS. EAE is an experimental disease in which animals are sensitized to brain products, and as a result develop varying degrees of paralysis.

Experimental allergic encephalomyelitis has now been conclusively proven to be a true model for ADEM, but not yet for MS. Detailed analyses reveal distinct differences between MS histology and that of ADEM and EAE [4]. While ADEM and EAE are comparable disorders, MS is shown to be a different disease. This is further attested to by the failure of large epidemiological studies to show an association between MS and other autoimmune disorders [5].

These significant data seem to have been ignored by some researchers, who are willing to defend the theory that MS is an autoimmune disease mediated by immunopathological mechanisms despite the overwhelming evidence to the contrary [6]. Over the past 60 years, a huge literature has accumulated claiming immunological abnormalities in MS, despite the failure of repeated attempts to confirm such data.

Clinical trials in MS

The importance of the acceptance of EAE as the putative model lies in the fact that most of the therapeutic trials in MS are based on this assumption. Each and every component of the immune system has been extensively investigated in EAE to support the autoimmunity theory for MS. The abnormal lymphocyte and cellular immune functions found in the brains of murine models with EAE have been accepted as the analogue of what is occurring in humans with MS [7]. The dominance of the autoimmune view is

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demonstrated by the abundance of published clinical trials based on it – "a rise from 50 such papers in 1965 to more than 300 by the year 2000" [4]. Of the 487 clinical trials for MS currently published on the NIH website [101], 94 are open studies testing various drug interventions. Of these 94, 30 are testing drugs for pain relief, spasticity, memory retrieval, depression and fatigue. The remaining 64 are testing immunomodulatory drugs founded on the hypothesis that EAE is the model for MS and that MS is an autoimmune disorder [102,103].

Trial design difficulties

An overview of the therapeutic trials is disappointing, as there are some significantly striking anomalies. In some reports, researchers disagreed about methodology, in other trials the placebo group did significantly better than the group taking the active drug [8,9]. Further anomalies can be found in the data from IFN-β and glatiramer trials [9]. Studies of these agents showed that "the inability to go beyond the 33% line raised the possibility the entire observed benefit is only a placebo effect, and that the significant deviation from the true placebo might be the outcome of partial unblinding of patients by the side effects. Moreover, reduction of relapse rate does not necessarily correlate with slower disability progression, and the use of standard MRI as secondary outcome measure is also controversial, as burden of disease and disease activity correlate weakly, if not at all, with disability" [9].

> "While acute disseminated encephalomyelitis and experimental allergic encephalomyelitis are comparable disorders, multiple sclerosis is shown to be a different disease."

Furthermore, in a recent review of the possible benefits of interferon in relapsing–remitting MS, the *Cochrane* Review drew attention to 208 articles, of which only seven met all the selection criteria and formed the subject of their conclusions. The variable quality of the trials, the inadequate methodology, the very high proportion and incomplete description of drop-outs, and the failure to adhere to the strict original intentions of the trial seriously detract from any claims that were made. The authors stated that these trials should be considered as single- rather than double-blind. They drew attention to the fact that if interferon-treated patients who had been removed from the study were deemed to have worsened, the significance of the reported effects was, therefore, lost. The efficacy of interferon on both exacerbations and on progression of the disease was modest after 1–2 years [10].

Side effects of the immunosuppressive drugs

The trials are vast and varied, but it is important to realize that when the multitude of results are analyzed, it can be seen that not one single patient has been cured. There is high morbidity, often with mortality, and highly sophisticated statistics are needed to detect clinical benefit [11]. The danger of using such powerful immunosuppressive drugs in these trials has been emphasized by the development of bizarre and rare complications. These include progressive multifocal leukoencephalopathy, malignant melanoma and other tumors [12,13]. Malignant melanoma has been emphasized, since the biology of melanocyte division is atypical and suggests an abnormality of neural crest-derived material. Due to the low incidence, some authors consider the occurrence of melanoma in MS to be coincidental. However, the coexistence of three tumors, including melanoma, of neural crest origin adds support to our hypothesis that MS is a cristopathy, and that the association with melanoma in patients on immunosuppressive treatment may be real [14–16].

> "Over the past 60 years, a huge literature has accumulated claiming immunological abnormalities in multiple sclerosis, despite the failure of repeated attempts to confirm such data."

Despite these apparent malignant effects, the number of researchers involved in forthcoming, current or ongoing similar trials has not decreased [17,102,103]. In previous and present commentaries on these trials, researchers are "optimistic that the coevolution of our understanding of the pathogenesis of MS and of the mechanisms of the various therapies, together with the development of more sophisticated MRI and laboratory markers, will lead to further improvement of trial design, and eventually treatment" [17]. They are not deterred by their own analysis of the disappointing results of such therapeutic studies. Indeed, "Especially informative are trials with therapies that not only turn out to be ineffective, but seem to make MS worse". They state that "The search must go on … for a therapeutic agent" [17]. Others do not share such optimism and view these interpretations [18] as wishful science fiction [4].

The costs

The cost in misery, morbidity and mortality for humans in these trials cannot be measured. Even 15 years ago, Gulcher *et al.* commented: "it could be argued that over the years the autoimmune hypotheses have been harmful to a considerable number of patients" [19]. Given such data, as has been presented in this article, it is very difficult to understand why this theory of the pathogenesis of MS has monopolized MS research.

A partial explanation might be found in the factor of the normal lifespan that MS patients can expect, accompanied by a high cost for their treatment. It is estimated that €12.5 billion is spent on MS in Europe annually, and that €2.5 billion is spent annually on drugs for treatment. This is for an estimated 380,000 MS patients in 28 European countries [20]. The recent decision to discontinue the dirucotide trial in the huge BioMS and Eli Lilly study is a welcome sign that researchers can no longer accept the therapeutic endeavors based on the autoimmune model [104]. Although the failure of the trial does not prove anything conclusively either way, it gives the message that basic studies on speculative immunological mechanisms are continually shown to be unrewarding.

A fruitful journey ahead

Out of such pessimism a more fruitful and rewarding journey lies ahead for researchers, particularly when taking into account the recent encouraging results in the field of glial studies and of

diagnostic imaging to plot myelin pathology *in vivo* [21,22]. There are certain associations that have been neglected. Namely, the association of malignant glioma [4] and of Schwann cell abnormalities (peripheral nerve) with MS [23]. These suggest that MS has a neural crest origin, and that a developmental abnormality plays a significant role in the pathogenesis of the disease.

A closer relationship between the laboratory and the clinic, and alternate viewpoints on the prime pathology, the association of MS with diseases of Schwann cells, are needed. The vast and growing literature on trophic factors and molecular development abnormalities operating locally and distally holds potential rewards. It is clear that modern research should move away from the autoimmunity theory and look to the exciting advances in glial cell research and in the cristopathies. In this regard, there are researches just beginning in the application of neurotrophic factors to MS when compared with the many trials of immunosuppressive drugs. The single trial of neurotrophic factors carried out by Frank *et al.* showed that while recombinant IGF-1 was ineffective, this drug was tolerated, and suggested a proposed mechanism of future trials with similar substances in MS [24].

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